论 著

MRI联合血清TNC、ITIH4对类风湿关节炎的诊断价值*

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【摘要】**目的** 探究磁共振成像(MRI)联合血清肌腱蛋白C(TNC)、α胰蛋白酶H4重链(ITIH4)对类风湿关节炎(RA)的诊断价值。**方法** 选取我院2022年10月至2023年10月收治的RA患者106例(RA组)，同期骨关节炎(OA)患者110例(OA组)，体检健康者110例(正常组)。酶联免疫吸附法检测血清TNC、ITIH4水平，并对患者进行MRI检查。ROC曲线分析血清TNC、ITIH4水平对RA的诊断价值，四表格分析MRI联合血清TNC、ITIH4水平对RA的诊断价值。**结果** RA组血清TNC水平高于OA组和正常组，ITIH4水平低于OA组和正常组(均*P*<0.05)；OA组血清TNC水平高于正常组，ITIH4水平低于正常组(均*P*<0.05)。血清TNC水平对RA诊断的AUC为0.817，敏感性和特异性为74.53%，75.45%，其诊断RA的结果与诊断标准具有一致性(Kappa值=0.500，*P*<0.001)。血清ITIH4水平对RA诊断的AUC为0.802，敏感性和特异性为74.53%，77.27%，诊断RA的结果与诊断标准具有一致性(Kappa值=0.518，P<0.001)。MRI诊断共正确检出OA患者84例，RA患者86例，其诊断RA的敏感性为81.13%(86/106)，特异性为76.36%(84/110)，准确度为78.70%(170/216)，阳性预测值为76.79%(86/112)，阴性预测值为80.77%(84/104)，MRI诊断RA结果与诊断标准具有一致性(Kappa值=0.574，*P*<0.001)。血清TNC、ITIH4联合MRI诊断RA的敏感性、特异性和准确度分别为98.11%(104/106)、75.45%(83/110)和86.57%(187/216)，三者联合诊断RA的结果与诊断标准的一致性较高(Kappa值=0.733，*P*<0.001)。血清TNC、ITIH4水平联合MRI诊断RA的敏感性和准确度较高，优于TNC、ITIH4和MRI单独诊断(*P*<0.005)。**结论** MRI联合血清TNC、ITIH4诊断RA具有较高准确度，可能对RA早期诊断具有一定价值。

【关键词】磁共振成像；肌腱蛋白C；
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Diagnostic Value of MRI Combined with Serum TNC and ITIH4 for Rheumatoid Arthritis*

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ABSTRACT
Objective To explore the diagnostic value of magnetic resonance imaging (MRI) combined with serum Tenascin-C (TNC) and inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) for rheumatoid arthritis (RA). ***Methods*** From October 2022 to October 2023, 106 RA patients (RA group), 110 osteoarthritis (OA) patients (OA group), and 110 healthy individuals (normal group) were selected from our hospital. Enzyme linked immunosorbent assay (ELISA) was applied to detect serum levels of TNC and ITIH4, and MRI examination was performed on patients. ROC curve was applied to analyze the diagnostic value of serum TNC and ITIH4 levels for RA. Four grid table method were applied to analyze the diagnostic value of MRI combined with serum TNC and ITIH4 levels for RA. ***Results*** The serum TNC level in the RA group was higher than that in the OA group and normal group, while the ITIH4 level was lower than that in the OA group and normal group (both *P*<0.05). The serum TNC level in the OA group was higher than that in the normal group, while the ITIH4 level was lower than that in the normal group (all *P*<0.05). The AUC of serum TNC level for the diagnosis of RA was 0.817, with sensitivity and specificity of 74.53% and 75.45%, the diagnostic results of RA were consistent with the diagnostic criteria (Kappa value=0.500, *P*<0.001). The AUC of serum ITIH4 level for the diagnosis of RA was 0.802, with sensitivity and specificity of 74.53% and 77.27%, the diagnostic results of RA were consistent with the diagnostic criteria (Kappa value=0.518, *P*<0.001). A total of 84 patients with OA and 86 patients with RA were correctly diagnosed by MRI. The sensitivity of diagnosing RA was 81.13% (86/106), specificity was 76.36% (84/110), accuracy was 78.70% (170/216), positive predictive value was 76.79% (86/112), and negative predictive value was 80.77% (84/104), the MRI diagnosis for RA was consistent with the diagnostic criteria (Kappa value=0.574, *P*<0.001). The sensitivity, specificity, and accuracy of serum TNC and ITIH4 combined with MRI in diagnosing RA were 98.11% (104/106), 75.45% (83/110), and 86.57% (187/216), respectively, the consistency between the results of the combined diagnosis of RA and the diagnostic criteria was high (Kappa value=0.733, *P*<0.001). The combination of serum TNC and ITIH4 levels with MRI had higher sensitivity and accuracy in diagnosing RA, and was superior to TNC, ITIH4, and MRI individual diagnoses (*P*<0.05). ***Conclusion*** MRI combined with serum TNC and ITIH4 has high accuracy in diagnosing RA, and may have certain value for early diagnosis of RA.
Keywords: Magnetic Resonance Imaging; Tenascin-C; Inter-alpha-trypsin Inhibitor Heavy Chain H4; Rheumatoid Arthritis

类风湿关节炎(rheumatoid arthritis, RA)是一种慢性炎症性疾病，涉及双侧多个关节，其特点是肌腱炎症引发的软骨破坏和骨侵蚀，患者可能出现严重的全身表现，若不及时治疗，可能导致功能丧失或残疾等[1]。预测性生物标志物和早期诊断工具在RA的治疗管理中至关重要。超声、磁共振成像(magnetic resonance imaging, MRI)和临床生物标志物常被推荐用于辅助诊断和监测RA患者的疾病状态。MRI能检测关节炎症，预测疑似关节痛患者的关节炎发展，且具有一定准确性[2]。但其耗时较长，成本相对较高，易受人为影响，且对膝关节诊断敏感性差。肌腱蛋白C(tenascin-C, TNC)是一种胞外基质蛋白，在RA患者血液中高度表达，且在晚期水平更高，其可能催化促炎因子合成和组织纤维化，影响组织重塑和形态变化，参与RA的发病机制[3]。既往报道，TNC在健康个体循环中几乎不存在，但在炎症环境(如RA)中高度表达，其能调节胞外基质蛋白的免疫稳态，通过特异性免疫反应在RA亚群的临床表现和关节损伤中起重要作用[4]。α胰蛋白酶H4重链(inter-alpha-trypsin inhibitor heavy chain H4, ITIH4)是一种血浆蛋白，由肝脏合成和分泌，其表达可能受急性炎症影响，在RA患者血液中特异性表达，且随RA患者的疾病活动度而波动，可能作为关节炎的血清特异性标志物[5]。但是，MRI、血清TNC、ITIH4水平对RA的诊断价值仍不清楚。因此，本研究选择对RA患者血清TNC、ITIH4水平进行检测，并联合MRI分析三者对RA的诊断价值，旨在为RA的早期检测和精准治疗提供依据。

1 资料与方法

1.1 一般资料 选取我院2022年10月至2023年10月收治的RA患者106例(RA组)，同期骨关节炎(OA)患者110例(OA组)，体检健康者110例(正常组)。三组临床资料见表1，比较

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差异均无统计学意义(*P*>0.05)。研究已经医院伦理委员会审核，受试者临床资料完整，均签署同意书。

纳入标准：RA患者符合RA相关诊断标准[6]；均为单侧病变；OA患者符合OA相关诊断标准[7]；均经MRI检查；正常组无影响该研究指标相关疾病。排除标准：其它感染性、免疫性疾病；高血压、糖尿病、肿瘤等；肝、肾、心功能障碍；关节手术史；血液系统障碍；关节发育异常或骨质损坏。

1.2 方法

1.2.1 MRI检查 应用Siemens Magnetom Skyra 3.0T磁共振成像系统(德国，西门子医疗)，取仰卧位扫描。常规平扫后扫描T2WI TSE、T1WI SE冠状位(TR/TE=500/25ms)、矢状位(TR/TE=3000/25ms)以及T2WI FSE脂肪抑制(TR/TE=3650/90ms)，层厚3mm，间距0.3mm。增强扫描(TR/TR/TI=10.308/2.052/28ms)，层厚1mm，间距3mm，FOV 240mm×240mm。由两名医师根据图像对患者滑膜炎、关节软骨损伤、半月板异常、骨侵蚀和骨髓水肿等检查结果进行分析。其中关节软骨变薄，关节积液，半月板损伤，Hoffa滑膜炎等为OA，关节滑膜增厚，软骨面毛糙等为RA[8-9]。

1.2.2 酶联免疫吸附法检测血清TNC、ITIH4水平 抽取健康者体检时和患者入院时静脉血3mL，离心取血清，与标准液分别置于酶标包被板，封板温育，加酶标试剂继续温育，30min后加显色剂，终止反应并检测450nm吸光度。通过标准曲线计算血清TNC、ITIH4水平。

1.3 统计学方法 采用SPSS 25.0分析数据，计数资料以n(%)描述，用χ^2检验；计量资料以($\bar{x}\pm s$)描述，用t检验，ROC曲线分析血清TNC、ITIH4水平对RA的诊断价值，四表格分析MRI联合血清TNC、ITIH4水平对RA的诊断价值。*P*<0.05为差异有统计学意义。

2 结 果

2.1 正常组、OA组、RA组血清TNC、ITIH4表达水平 RA组血清TNC水平高于OA组和正常组，ITIH4水平低于OA组和正常组(均*P*<0.05)；OA组血清TNC水平高于正常组，ITIH4水平低于正常组(均*P*<0.05)。见表2。

2.2 血清TNC、ITIH4水平对RA诊断价值 ROC曲线结果显示，血清TNC水平对RA诊断的AUC为0.817，敏感性和特异性为74.53%，75.45%，其诊断RA的结果与诊断标准具有一致性(Kappa值=0.500，*P*<0.001)。血清ITIH4水平对RA诊断的AUC为0.802，敏感性和特异性为74.53%，77.27%，诊断RA的结果与诊断标准具有一致性(Kappa值=0.518，*P*<0.001)。见图1，表3。

表1 三组临床资料分析 [n(%)]

组别	例数	年龄(岁)	BMI(kg/m²)	性别		病程(月)
				男	女	
正常组	110	53.88±5.56	24.01±2.45	50(45.45)	60(54.55)	-
OA组	110	53.51±5.43	23.79±2.51	54(49.09)	56(50.91)	4.65±0.83
RA组	106	54.15±5.57	24.26±2.58	43(40.57)	63(59.43)	4.52±0.76
F/χ^2/t值	-	0.367	0.945	1.593		1.199
*P*值	-	0.693	0.390	0.451		0.232

表2 正常组、OA组、RA组血清TNC、ITIH4表达水平

组别	例数	TNC(ng/mL)	ITIH4(μg/mL)
正常组	110	32.61±7.24	195.72±31.33
OA组	110	84.23±19.68*	119.61±23.36*
RA组	106	110.47±21.26*#	91.82±23.03*#
F值	-	576.247	457.062
*P*值	-	＜0.001	＜0.001

注：与正常组比，*P<0.05；与OA组比，#P<0.05。

表3 血清TNC、ITIH4水平对RA诊断价值

项目	AUC	95%CI	截断值	约登指数	敏感性(%)	特异性(%)
TNC	0.817	0.759~0.866	96.03 ng/mL	0.500	74.53	75.45
ITIH4	0.802	0.743~0.853	104.75 μg/mL	0.518	74.53	77.27

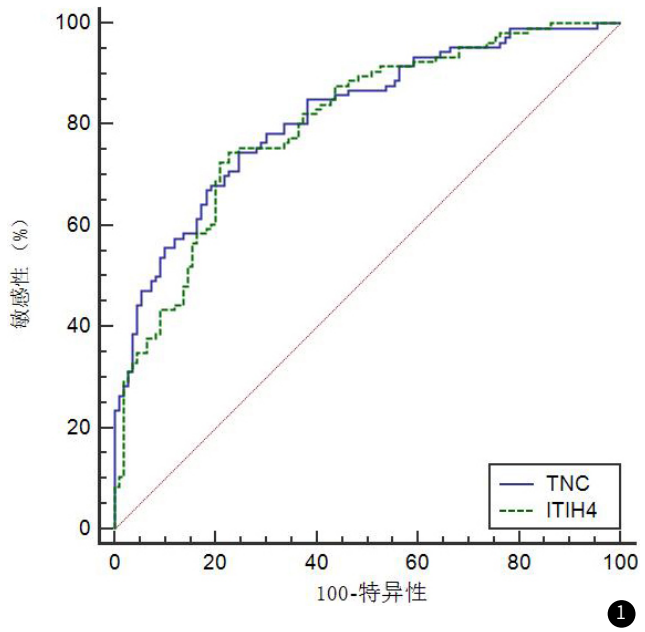

图1 血清TNC、ITIH4水平诊断RA的ROC曲线。

2.3 OA组和RA组MRI检测结果分析 MRI诊断结果表明，两组骨髓水肿、骨侵蚀、关节软骨缺损、滑膜炎、半月板异常发生率比较，差异有统计学意义(均*P*<0.05)。见表4。MRI诊断共正确检出OA患者84例，RA患者86例。检出RA的敏感性为81.13%(86/106)，特异性为76.36%(84/110)，准确度为78.70%(170/216)，阳性预测值为76.79%(86/112)，阴性预测值为80.77%(84/104)。MRI诊断RA结果与诊断标准具有一定一致性(Kappa值=0.574，*P*<0.001)。见表5。

2.4 血清TNC、ITIH4水平联合MRI对RA诊断价值 以血清TNC、ITIH4水平诊断RA的最佳截断值(96.03 ng/mL、104.75 μg/mL)作为临界值，当诊断时患者血清TNC＞96.03 ng/mL或当ITIH4≤104.75 μg/mL时，推断患者为RA，否则为OA。在进行血清TNC、ITIH4水平和MRI联合诊断时，采用并联方式进行检测，当血清TNC、ITIH4和MRI中任意一项诊断结果为RA，则推断患者为RA，当血清TNC、ITIH4和MRI三者诊断结果均为OA时，则推断患者为OA。结果显示，血清TNC、ITIH4联合MRI诊断RA的敏感性、特异性和准确度分别为98.11%、75.45%和86.57%，三者联合诊断RA的结果与诊断标准的一致性较高(Kappa值=0.733，*P*<0.001)。血清TNC、ITIH4水平联合MRI诊断RA的敏感性和准确度较高，优于TNC、ITIH4和MRI单独诊断(均*P*<0.05)。见表6。

表4 比较MRI检测OA组和RA组关节常见症状发生率 [n(%)]

组别	例数	骨髓水肿	骨侵蚀	关节软骨缺损	半月板异常	滑膜炎
OA组	110	56(50.91)	53(48.18)	95(86.36)	87(79.09)	95(86.36)
RA组	106	72(67.92)	90(84.91)	5(4.72)	0(0.00)	78(73.58)
χ^2值	-	6.474	32.538	144.734	140.377	5.529
*P*值	-	0.011	＜0.001	＜0.001	＜0.001	0.019

表5 OA组和RA组MRI检测结果分析

组别	MRI诊断结果	
	OA(n=104)	RA(n=112)
OA组(n=110)	84	26
RA组(n=106)	20	86
Kappa值	0.574	
*P*值	＜0.001	

表6 血清TNC、ITIH4水平联合MRI对RA的诊断效能

诊断方法	敏感性	特异性	准确度
MRI检查	81.13%(86/106)*	76.36%(84/110)	78.70%(170/216)*
血清TNC	74.53%(79/106)*	75.45%(83/110)	75.00%(162/216)*
血清ITIH4	74.53%(79/106)*	77.27%(85/110)	75.93%(164/216)*
三者联合	98.11%(104/106)	75.45%(83/110)	86.57%(187/216)

注：与三者联合比较，*P<0.05。

3 讨　论

RA是一种复杂的多因素自身免疫性病变，发病隐匿，进展缓慢，主要累及关节，也可损害关节外器官，包括皮肤、眼睛、心脏等，其常与慢性炎症过程相关，可能由遗传、环境和随机因素引起，但具体病理生理机制尚未阐明[10]。研究发现，RA影响全球人数的0.5%~1.0%，其与进行性残疾、全身并发症和早期死亡有关，且具有累积终生和遗传风险[11]。因此，临床上及时和准确的诊断在RA治疗中非常重要，可以预防和缓解多数患者的疾病进展。目前，临床常选择影像学、实验室标志物等对RA患者进行诊断和监测。而本研究选择MRI和血清TNC、ITIH4联合进行诊断，分析其对RA的诊断价值。

MRI是临床检测RA患者早期变化最合适的成像方法，其能通过检测亚临床炎症预测RA的发展，且具有一定敏感性和可靠性[12]。研究显示，MRI在疑似或确诊的RA中，能监测软骨损伤、骨侵蚀等所有相关病理，在预测RA发展，监测RA患者疾病活动性和关节破坏方面具有较好敏感性[13]。庞琳烜等[14]表明，MRI对RA患者关节积液、骨膜炎和骨侵蚀的检出率较高，对早期RA的诊疗具有明确应用价值。卢昊宁等[15]发现，MRI诊断早期RA的敏感度、特异性和准确度分别为93.33%、85.00%和89.17%，其与血清CTHRC1、sPD-1联合诊断的敏感性为91.70%，MRI联合血清诊断可能对早期RA的诊断具有一定价值。本研究中，MRI诊断共正确检出RA患者86例，其诊断RA的敏感性为81.13%，特异性为76.36%，准确度为78.70%，阳性预测值和阴性预测值分别为76.79%、80.77%。MRI诊断RA结果与诊断标准具有一致性，说明MRI能有效检出RA患者病理特点，对RA诊断具有重要价值。张翠景等[16]通过对148例RA患者进行MRI检查，发现滑膜炎、肌腱腱鞘炎、关节积液和骨侵蚀的检出率分别为89.96%、52.03%、77.03%和70.95%，MRI对RA具有一定诊断价值，但其存在可重复性差，诊断图像单一等不足，易受多种因素影响，临床应用具有一定局限性。因此可选择将其与血清指标联合，以增强其优势，避免不足。

TNC作为一种糖蛋白，具有促炎特性，是RA中重要的瓜氨酸化抗原，在自身免疫性疾病的炎症反应中高度表达，其高表达与RA患者疾病活动相关，在RA患者体内被CD4 T细胞和B细胞识别，可能放大自身免疫并促进RA的发生和进展[17]。既往报道，TNC与RA患者炎症介质水平相关，受到miR-494的负调控，并与NF-κB通路有关，其下调能减弱巨噬细胞炎症，最终推动关节炎炎症的缓解[18]。李丽等[19]表明，RA模型大鼠中TNC表达升高，白藜芦醇可以明显抑制TNC表达，下调TLR4和炎症因子水平，减缓炎症，改善RA症状。Dominic等[20]发现，TNC与RA的病理生理学有关，其在血清RA患者中上调，其诊断RA的AUC为0.98，且敏感性为96.60%，可能有助于识别大量RA患者。本研究发现，RA患者血清TNC水平高于OA患者和健康人群，血清TNC水平诊断RA的AUC为0.817，敏感性和特异性为74.53%，75.45%，其诊断RA的结果与诊断标准具有一致性。提示TNC对RA具有一定诊断价值，可能用于早期RA的诊断。

ITIH4是抗炎标志物，在炎症、伤口愈合、细胞增殖等中具有有益作用，能通过相关信号通路参与调节炎症和结缔组织修复愈合过程[21]。He等[22]报道，ITIH4能调节炎症和免疫，在RA患者中表达下调，并与炎症因子表达负相关，可能参与RA的炎症反应，其治疗后水平逐渐增加，与RA患者的治疗反应和缓解有关，检测其循环水平对临床RA的疾病风险、疾病活动度、炎症和治疗结果的监测具有一定作用。Iwai等[23]发现，ITIH4在血清中以蛋白形式表达，可能发生瓜氨酸化，其不能改变关节炎的严重程度，但可能通过调节中性粒细胞表达参与机体免疫性炎症反应。本研究分析了RA患者血清中ITIH4表达，表明RA患者ITIH4水平较低，其诊断RA的AUC为0.802，敏感性和特异性为74.53%，77.27%，诊断RA的结果与诊断标准具有一致性，提示ITIH4可能在一定程度上诊断早期RA。血清TNC、ITIH4联合MRI诊断RA的敏感性、特异性和准确度分别为98.11%、75.45%和86.57%，三者联合诊断RA的敏感性和准确度较高，优于TNC、ITIH4和MRI单独诊断，且联合诊断RA的结果与诊断标准的一致性较高，表明血清TNC、ITIH4联合MRI能提高RA诊断的准确性，对RA具有较好诊断价值。

综上所述，MRI联合血清TNC、ITIH4诊断RA具有较高准确度，可能对RA早期诊断具有一定价值。但纳入病例较少，研究范围有限，后续将扩大样本范围继续分析，并探索其潜在机制。

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