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类风湿关节炎患者血浆外泌体下调miRNA的差异表达及其临床诊断价值研究

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摘 要

目的：探讨类风湿关节炎(RA)患者血浆外泌体中miR-200a-3p、miR-133a-3p、miR-3960及miR-184-3p的表达水平及其在RA早期诊断和病情活动度监测中的临床意义。方法：选取2023年1月至2024年12月于安徽医科大学第一附属医院就诊的30例RA患者(活动组20例，稳定组10例)及20例健康对照(HC)。采用超速离心法及试剂盒法提取血浆外泌体，并通过透射电镜(TEM)、纳米粒径分析及标志蛋白(CD9、CD81)进行鉴定。利用高通量测序筛选差异miRNAs，并应用qRT-PCR对候选下调miRNAs进行扩大样本验证。分析各miRNA表达水平与临床指标(DAS28-CRP、CRP等)的相关性，并采用ROC曲线评价其诊断效能。结果：成功分离并鉴定出符合特征的血浆外泌体。qRT-PCR结果显示，RA患者血浆外泌体中miR-200a-3p、miR-133a-3p、miR-3960及miR-184-3p的表达水平均显著低于HC组(均$P < 0.001$)。其中，miR-200a-3p、miR-133a-3p、miR-184-3p在活动期RA组中的表达显著低于稳定组(均$P < 0.01$)，且与DAS28-CRP及CRP呈负相关。ROC曲线显示，miR-200a-3p、miR-133a-3p、miR-184-3p三者联合诊断的AUC为0.921，灵敏度86.0%，特异度88.0%。结论：RA患者血浆外泌体中存在显著下调的miRNA谱，miR-200a-3p、miR-133a-3p和miR-184-3p可作为评估RA疾病诊断及病情活动性的潜在无创生物标志物。

关键词

类风湿性关节炎，微小RNA，外泌体，生物标志物

Differential Expression of Downregulated miRNAs in Plasma Exosomes of Rheumatoid Arthritis Patients and Their Clinical Diagnostic Value

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Abstract

Objective: To investigate the expression levels of miR-200a-3p, miR-133a-3p, miR-3960, and miR-184-3p in plasma exosomes of rheumatoid arthritis (RA) patients and their clinical significance in early diagnosis and disease activity monitoring. Methods: A total of 30 RA patients (20 in the active group and 10 in the stable group) and 20 healthy controls (HC) were selected from the First Affiliated Hospital of Anhui Medical University between January 2023 and December 2024. Plasma exosomes were isolated using ultracentrifugation and reagent kits, and characterized by transmission electron microscopy (TEM), nanoparticle size analysis, and marker proteins (CD9, CD81). High-throughput sequencing was performed to identify differential miRNAs, and qRT-PCR was used to validate the expression of candidate downregulated miRNAs in an expanded sample. The correlation between miRNA expression levels and clinical parameters (DAS28-CRP, CRP, etc.) was analyzed, and ROC curves were used to assess their diagnostic efficiency. Results: Plasma exosomes with characteristic features were successfully isolated and identified. qRT-PCR results showed that the expression levels of miR-200a-3p, miR-133a-3p, miR-3960, and miR-184-3p in plasma exosomes of RA patients were significantly lower than those of the HC group (all $P < 0.001$). Among them, miR-200a-3p, miR-133a-3p, and miR-184-3p were significantly lower in the active RA group compared to the stable group (all $P < 0.01$), and were negatively correlated with DAS28-CRP and CRP. ROC analysis showed that the combined diagnostic AUC of miR-200a-3p, miR-133a-3p, and miR-184-3p was 0.921, with a sensitivity of 86.0% and a specificity of 88.0%. Conclusion: A significantly downregulated miRNA profile exists in plasma exosomes of RA patients. miR-200a-3p, miR-133a-3p, and miR-184-3p could serve as potential non-invasive biomarkers for evaluating RA diagnosis and disease activity.

Keywords

Rheumatoid Arthritis, microRNA, Exosomes, Biomarkers

1. 前言

类风湿关节炎(RA)是一种以慢性侵蚀性关节炎为特征的自身免疫性疾病[1]-[3]。目前临床常用的指标如 RF 及抗 CCP 抗体在早期诊断和病情动态监测方面仍存在一定局限性[4] [5]。外泌体(Exosomes)作为细胞间信息传递的重要载体，其包裹的 microRNAs (miRNAs)在体液中高度稳定，参与调控多种免疫炎症通路[6]。既往研究多关注上调的 miRNA [7]，本研究通过高通量测序筛选并验证 RA 患者血浆外泌体中显著下调的 miRNAs，旨在探索其作为新型生物标志物的临床价值。

2. 材料与方法

2.1. 研究对象

选取 2023 年 1 月至 2024 年 12 月在我院风湿免疫科就诊的 30 例 RA 患者。纳入标准符合 1987 年 ACR 修订标准。根据 DAS28-CRP 评分分为活动组(≥3.2, n = 20)和稳定组(<2.6, n = 10)。另选 20 例健康体

检者作为健康对照组(HC)。本研究方案符合安徽医科大学第一附属医院伦理委员会关于人体生物医学研究的伦理规范，已获得该委员会批准。全部研究对象在入组前均签署书面知情同意书。

2.2. 外泌体分离与鉴定

采用超速离心法或 exoEasy 试剂盒提取血浆外泌体。通过 HT-7800 投射电镜观察形态，Flow Nano-Analyzer 进行粒径分析，Western Blot 检测标志蛋白 CD9、CD81 及 TSG101 的表达。

2.3. 建库测序及差异 miRNA 的筛选

在筛选阶段，对 RA 组(n = 6)及健康对照组(n = 6)外泌体 RNA 进行 small RNA 测序。提取的 RNA 样本送至深圳华大基因科技服务有限公司完成文库构建及高通量测序。实验流程、试剂使用及仪器操作均按照标准规范执行。小 RNA 文库制备、测序及后续生物信息学分析由华大基因(BGI，中国)承担，测序平台为 BGISEQ-500。根据测序结果，差异表达分析使用 DESeq2 软件。以 $P < 0.05$ 且倍数变化(fold change) > 1.5 为阈值筛选上调与下调 miRNA。差异 miRNA 分析采用 DESeq2 方法，筛选标准为 $P < 0.05$ 且|Fold change| > 1.5。结合相关文献，选取 4 个显著下调的外泌体 miRNAs，进行扩大样本验证。

2.4. qRT-PCR 验证

使用 miRNAeasy 试剂盒提取总 RNA，加尾法反转录合成 cDNA 。采用 SYBR Green 法检测 miR-200a-3p、miR-133a-3p、miR-3960 及 miR-184-3p 的表达，以 U6 为内参，采用 2^-ΔΔCt 方法计算相对表达量($\Delta Ct = Ct\_target - Ct\_U6$；$-\Delta\Delta Ct = -$(样本 $\Delta Ct -$ 对照 ΔCt))。

2.5. 统计学方法

使用 SPSS27.0 软件对实验数据进行分析。所有计量资料均进行正态分布检验，符合正态分布的采用均数 ± 标准差($\chi \pm s$)表示；若方差齐性满足，采用 t 检验。两独立样本采用 t 检验。非正态分布数据则以 M (P25, P75)表示。变量间符合正态分布，多组对比采用单因素方差分析，相关性采用 Pearson 分析；非正态分布则两组对比采用 Mann-Whitney 秩和检验，多组对比采用 Kruskal Wallis 检验，相关性采用 Spearman 分析。当 $P < 0.05$ 时认为差异具有统计学意义。计数资料采用卡方检验，以 $\alpha = 0.05$ 为检验水平，当 $P < 0.05$ 时认为差异具有统计学意义。采用 ROC 曲线分析外泌体 miRNAs 对 RA 疾病的诊断价值，$P < 0.05$ 表示差异有统计学意义。

3. 结果

3.1. 研究对象一般资料及临床资料比较分析

Table 1. General information and clinical data of the research subjects
表 1. 研究对象一般资料及临床资料

指标	RA 组(n = 30)	HC 组(n = 20)	统计量($t/Z/\chi^2$)	P 值
年龄(mean ± SD，岁)	52.27 ± 10.10	46.60 ± 11.72	1.822	0.075
性别(女/男，n)	22/8	17/3	0.393	0.531
ESR [M (P25, P75), mm/h]	52.00 (11.25, 90.50)	5.30 (2.22, 10.00)	−4.198	<0.001
CRP [M (P25, P75), mg/L]	39.66 (10.25, 69.55)	3.75 (1.58, 5.78)	−4.484	<0.001
RF [M (P25, P75), IU/ml]	78.83 (14.93, 225.57)	5.90 (2.45, 11.55)	−4.444	<0.001
Anti-CCP [M (P25, P75), U/ml]	66.00 (11.50, 154.25)	6.00 (2.80, 11.00)	−3.676	<0.001

本研究验证阶段共纳入受试者 50 例，其中类风湿关节炎(RA)患者 30 例，健康对照(HC) 20 例。人口学资料分析显示，RA 组女性 22 例(73.3%)、男性 8 例(26.7%)，平均年龄为 52.27 ± 10.10 岁；HC 组女性 15 例(75.0%)、男性 5 例(25.0%)，平均年龄为 46.60 ± 11.72 岁。两组在年龄($t = 1.821$, $P = 0.556$)及性别构成($\chi^2 = 0.017$, $P = 0.896$)方面差异均无统计学意义，基线资料具有可比性(见表 1)。

3.2. 血浆外泌体差异基因表达分析

对筛选样本实施高通量转录组测序。高通量测序服务由深圳华大基因科技服务有限公司完成。KEGG 通路富集分析显示，在上调的 miRNA 中，MAPK 信号通路、Rap1 信号通路、cGMP-PKG 信号通路、Wnt 信号通路和 Ras 信号通路是富集最多的 5 条信号通路。在下调的 miRNA 中，MAPK 信号通路、Rap1 信号通路、cGMP-PKG 信号通路、催产素信号通路和 mTOR 信号通路是前 5 位富集的信号通路(见图 1)。

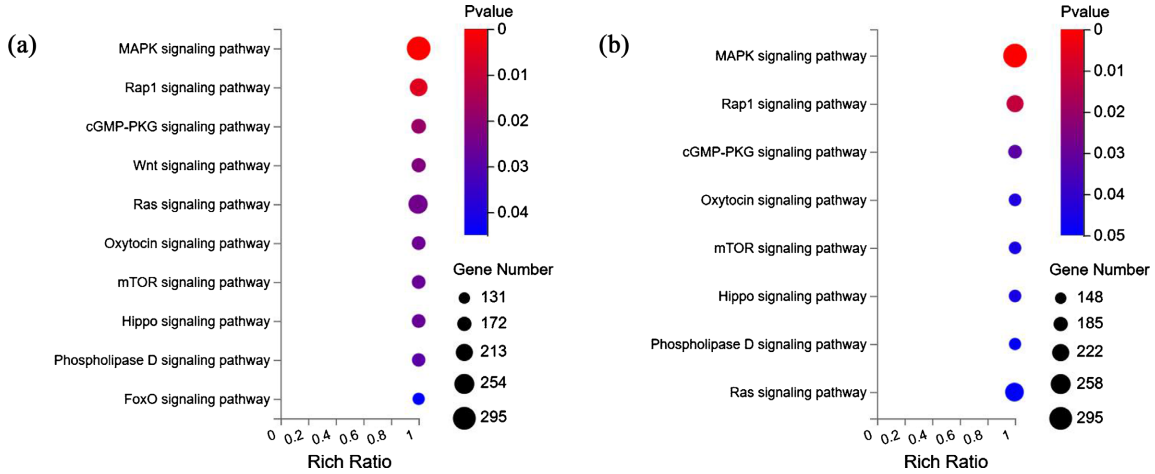


Figure 1. KEGG pathway analysis. (a) Upregulated; (b) downregulated
图 1. KEGG 通路富集分析。(a) 上调；(b) 下调

GO 分析显示：前 5 位有意义的分子功能分别是 ATP 结合、蛋白质结合、核苷酸结合、激酶活性和转移酶活性。前 5 位有意义的细胞组分为核质、胞浆、细胞核、细胞外外泌体和内泌体。前五个有意义的生物学过程术语是磷酸化、RNA 聚合酶 II 的负转录调控、蛋白质转运、细胞周期和蛋白质磷酸化。见图 2。

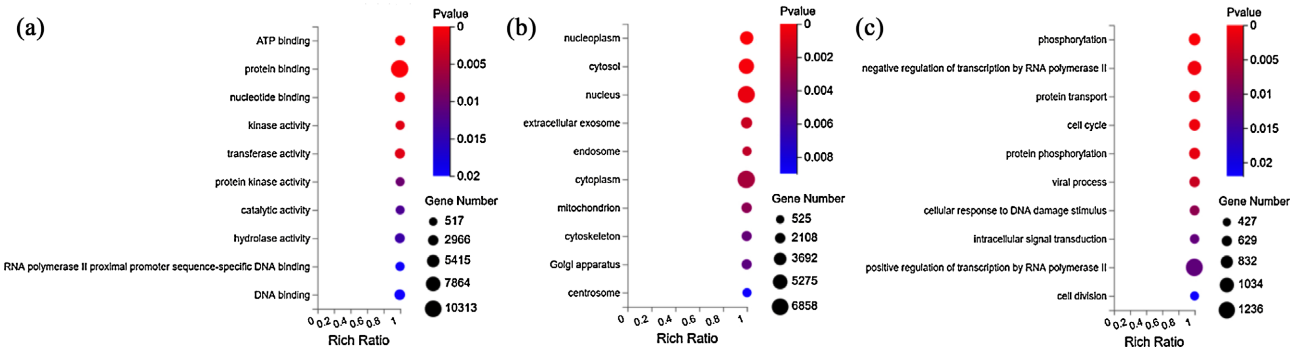


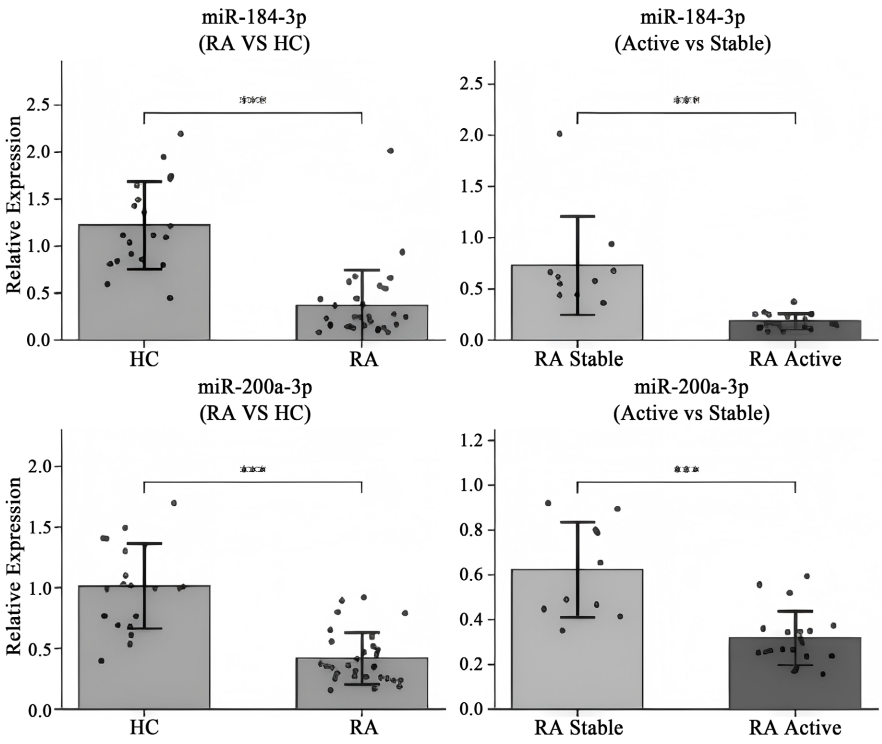
Figure 2. Targets of upregulated and downregulated differentially expressed exosomal miRNAs according to the GO analysis. Enriched GO terms in the molecular function (a), cellular component (b), and biological process (c) categories
图 2. 根据 GO 分析，外泌体差异表达 miRNAs 上调和下调的靶标。在(a) 分子功能、(b) 细胞成分和(c) 生物过程类别中富集了 GO 术语

3.3. 候选 miRNAs 的表达验证

qRT-PCR 结果显示：miR-184-3p 在 RA 组中的相对表达水平[0.27 (0.19, 0.43)]显著低于健康对照组[0.90 (0.77, 1.54)]的相对表达水平，差异具有统计学意义($Z = -5.31$, $P < 0.001$)。miR-184-3p 在 RA 活动组[0.22 (0.15, 0.28)]中的表达水平显著低于 RA 稳定组[0.60 (0.45, 0.75)]的相对表达水平，差异具有统计学意义($t = -5.42$, $P < 0.001$)。miR-200a-3p 在 RA 组[0.29 (0.21, 0.43)]的表达水平低于健康对照组[1.20 (0.84, 1.60)]，差异有统计学意义($Z = -4.310$, $P < 0.001$)；其在 RA 活动组[0.24 (0.14, 0.53)]中的表达水平明显低于 RA 稳定组[0.67 (0.266, 1.237)]，差异具有统计学意义($t = -2.42$, $P < 0.001$)。miR-133a-3p 在 RA 组[0.23 (0.19, 0.47)]的表达水平显著低于健康对照组 1.04 (0.74, 1.37)]，差异有统计学意义($Z = -4.37$, $P < 0.001$)；其在 RA 活动组[0.21(0.14, 0.32)]中的表达水平低于 RA 稳定组[0.57 (0.38, 0.87)]，差异具有统计学意义($t = -3.02$, $P < 0.001$)。miR-3960 在 RA 组[0.41 (0.28, 0.57)]的表达水平显著低于健康对照组 1.24 (0.84, 1.73)]，差异有统计学意义($Z = -3.37$, $P < 0.001$)；在 RA 活动组中位表达量为 0.38 (0.33, 0.45)，在 RA 稳定组为 0.43 (0.40, 0.47)，经 Mann-Whitney U 检验，差异无统计学意义($P = 0.262$, $P > 0.05$) (见图 3，表 2)。

Table 2. Analysis of the expression concentrations of 4 candidate exosomal miRNAs in plasma exosomes
表 2. 4 个候选外泌体 miRNAs 在血浆外泌体表达浓度分析

候选 miRNA	测序 GeneID	HC 均值	HC_SEM	log2 (RA/HC)	P 值	Q 值	HC 平均读数	RA 平均读数
miR-184-3p	novel-hsa-miR184-3p	1.086	0.914	−10.081	3.246	2.249	31.5	0
miR-200a-3p	hsa-miR-200a-3p	0.521	0.341	−9.025	4.270	2.263	16	0
miR-133a-3p	hsa-miR-133a-3p	4.114	4.084	−8.421	1.117	2.084	119.5	0.333
miR-3960	hsa-miR-3960	0.371	0.320	−8.535	2.624	1.116	9.5	0



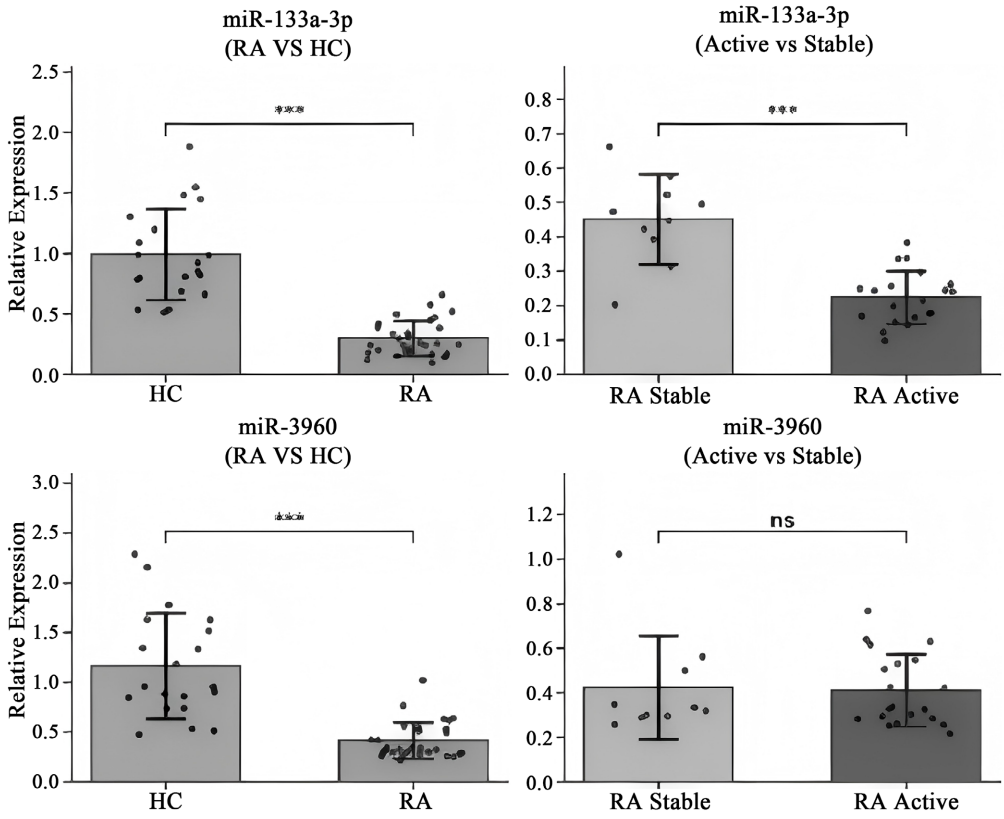


Figure 3. Comparison of relative levels of 4 plasma exosomal miRNAs between RA patients and control subjects
图 3. RA 患者和对照组之间 4 种血浆外泌体 miRNA 的相对水平比较

3.4. 相关性分析

Spearman 分析显示：miR-133a-3p 的表达水平与 DAS28-CRP、CRP、SJC28、TJC28 呈现显著负相关(均 $P<0.05$)，即肿胀疼痛关节数越多，病情活动度越高，miR-133a-3p 的表达水平越低，此外，miR-133a-3p 的表达水平与 RF 呈较弱负相关($r=-0.481$, $P<0.05$)，而 miR-133a-3p 与 ESR、Anti-CCP 及其他临床指标之间未观察到显著相关性(均 $P>0.05$) (见表 3)；miR-3960 的相对表达水平与 DAS28-CRP、ESR、CRP、SJC28、TJC28、RF、Anti-CCP 等临床指标之间均未观察到显著相关性(均 $P>0.05$)；miR-200a-3p 的相对表达水平与 DAS28-CRP、CRP、SJC28 及 TJC28 均呈负相关(均 $P<0.05$)，与 RF 及 ESR 呈弱负相关($P<0.05$)，miR-200a-3p 与其他临床指标之间未见显著相关性(均 $P>0.05$)；miR-184-3p 的相对表达水平与 DAS28-CRP 及 CRP 呈负相关(均 $P<0.05$)，miR-184-3p 与 ESR、关节计数、自身抗体水平等其他临床指标之间未观察到显著相关性(均 $P>0.05$)。

Table 3. The correlation between the relative expression levels of miRNAs in plasma exosomes of RA patients and clinical indicators
表 3. RA 患者血浆外泌体 miRNAs 相对表达水平与临床指标相关性

临床指标	miR-133a-3p		miR-200a-3p		miR-184-3p		miR-3960	
	r 值	P 值	r 值	P 值	r 值	P 值	r 值	P 值
RF	−0.481	0.046	−0.435	0.041	0.102	0.591	0.155	0.413
Anti-CCP	0.222	0.238	0.227	0.629	0.39	0.953	0.185	0.268

续表

ESR	0.337	0.069	−0.598	0.049	0.092	0.632	0.361	0.777
CRP	−0.535	0.002	−0.526	0.021	0−.581	0.003	0.079	0.713
DAS28-CRP	−0.426	0.018	−0.576	0.029	−0.363	0.047	0.037	0.877
TJC28	−0.467	0.009	−0.576	0.034	0.262	0.961	0.091	0.633
SJC28	−0.571	0.003	−0.492	0.031	0.208	0.271	0.033	0.875

3.5. 诊断效能评价

ROC 曲线显示各指标均具诊断价值：miR-200a-3p：在四种候选 miRNAs 中表现出最佳的诊断价值。其 AUC 达到 0.843 (95% CI: 0.730~0.937)，差异具有统计学意义($P < 0.001$)。在最佳截断值处，其诊断灵敏度为 76.7%，特异度为 84.7%，提示该指标在区分 RA 患者与健康人群方面具有较高的准确性，误诊和漏诊率相对较低。miR-133a-3p：亦显示出良好的诊断效能，AUC 为 0.802 (95% CI: 0.640~0.829, $P < 0.001$)。该指标的特异度较高(81.6%)，表明其在排除非 RA 人群方面表现较好；虽然灵敏度(69.7%)略低于 miR-200a-3p，但仍具备临床参考价值。相比之下，miR-184-3p 和 miR-3960 的单独诊断效能相对较弱，miR-184-3p：诊断效能中等，AUC 为 0.703 (95% CI: 0.556~0.837, $P < 0.05$)。其特异度尚可(77.2%)，但灵敏度仅为 57.3%，提示若单独使用该指标，可能存在一定的漏诊风险。miR-3960：在本研究队列中显示出的诊断价值相对有限，AUC 为 0.612 (95% CI: 0.515~0.785, $P < 0.05$)，尽管其灵敏度较高(73.3%)，但特异度较差(55.3%)，意味着单独检测容易产生假阳性结果(见图 4)。构建包含 miR-200a-3p、miR-133a-3p 和 miR-184-3p 的联合诊断模型，ROC 曲线分析显示，联合模型的 AUC 提升至 0.921，优于任一单项指标。在最佳截断值处其诊断灵敏度和特异度分别为 86.00%和 88.00%，表明多指标联合检测能有效提高 RA 的诊断效能。见图 4。

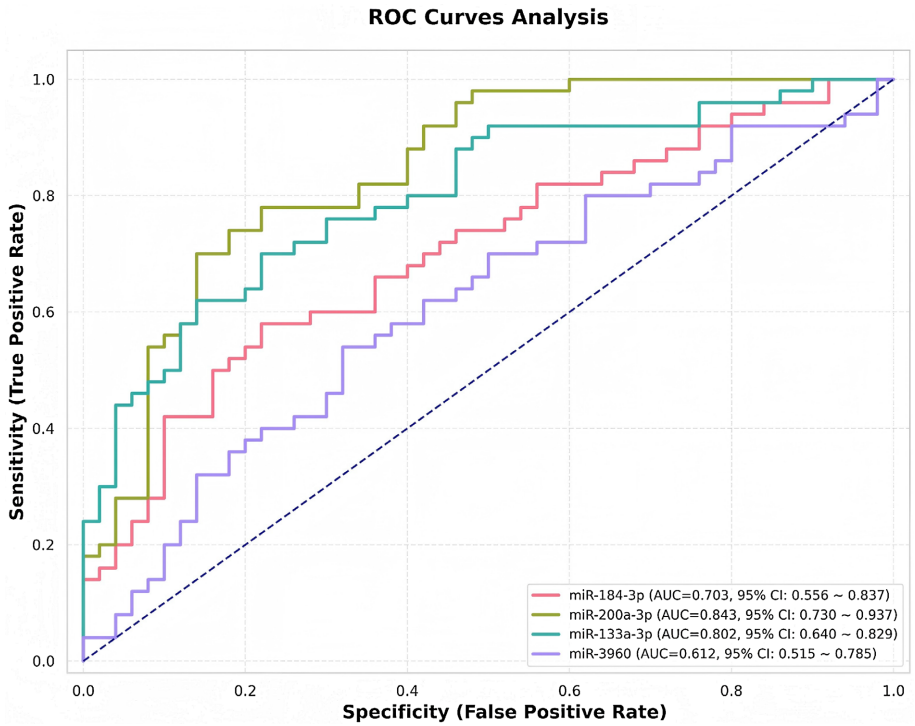


Figure 4. ROC curves
图 4. ROC 曲线图

4. 讨论

本研究证实了 RA 患者血浆外泌体中 miR-200a-3p、miR-133a-3p、miR-184-3p 和 miR-3960 呈显著下调表达。miR-200 家族被认为是上皮-间质转化的抑制因子，其下调可能解除对 FLS 细胞侵袭性的抑制，从而加剧关节破坏[8]-[10]。miR-133a-3p 的降低可能削弱其对促炎轴的“刹车”作用，导致全身炎症水平升高[11]-[13]。而 miR-3960 在 RA 中的稳定低表达可能更多地反映了慢性骨代谢受损的背景[14]。联合诊断模型显示出极高的诊断效能，提示外泌体 miRNA 组合有望成为 RA 辅助诊断及病情监测的新型工具[15]-[18]，特别是对于血清学阴性患者具有重要的参考价值[19]-[25]。本研究验证了部分结果，但仍存在一些局限性。本研究纳入的 RA 患者为 30 例，HC 为 20 例。虽然满足了统计学的基本要求且得出了显著性差异，但相对较小的样本量可能导致 ROC 曲线的置信区间较宽(如 miR-3960 的 95% CI 0.515~0.785)，限制了结论的普遍性，亚组分层时仍显单薄，结论的普适性需未来需扩大样本量进行多中心验证。本研究为横断面研究，横断面设计虽能揭示相关性，却无法确证因果关系，仅能通过相关性分析推测 miRNA 与疾病活动的关联。未来需依赖纵向队列观察这些 miRNA 随治疗好转的动态演变缺乏纵向随访数据，无法确证这些 miRNA 的水平是否会随着治疗好转而恢复正常，因此其作为疗效监测指标的价值尚需前瞻性队列研究证实。纳入的 RA 患者可能正在接受不同的 DMARDs 治疗，药物(如甲氨蝶呤或激素)本身可能影响外泌体的分泌或 miRNA 的表达[26]-[33]，本研究未对用药情况进行分层分析，这可能是一个混杂因素。本研究主要停留在现象描述和临床关联分析层面。关于 miR-200a-3p 是否确切靶向 ZEB1 调控 FLS 侵袭，以及 miR-3960 是否直接影响成骨细胞功能[34]-[39]，尚需通过体外细胞实验及动物模型进行分子机制验证。

5. 结论

类风湿关节炎(RA)患者与健康对照组在血浆外泌体 miRNA 表达谱上存在显著差异。本研究筛选并验证了四种候选下调 miRNA (miR-184-3p、miR-200a-3p、miR-133a-3p、miR-3960)，这些 miRNA 在 RA 患者的血浆外泌体中均显著下调。结果表明，与 RA 相关的外泌体 miRNA 通过抑制炎症反应的作用，可能促进炎症反应，从而参与 RA 的发病机制。此外，这些 miRNA 与疾病活动度(DAS28-CRP 评分)及炎症指标(如血沉、C-反应蛋白、类风湿因子等)呈负相关，进一步支持它们在 RA 病理过程中的重要调控作用。miR-184-3p、miR-200a-3p 和 miR-133a-3p 的下调与 RA 的疾病活动度和炎症负荷密切相关。这三种下调 miRNA 的相对表达水平与疾病活动度指标(DAS28-CRP)及炎症指标(如 CRP)呈显著负相关。进一步分析发现，miR-200a-3p 和 miR-133a-3p 与关节受累指标(如 SJC28、TJC28)呈负相关，并与部分免疫炎症指标(如类风湿因子、红细胞沉降率)表现出弱负相关。上述结果表明，这些 miRNA 可能参与 RA 的炎症放大作用和滑膜病变进展，并有助于反映患者的临床表型差异。miR-3960 在 RA 中显著下调，但与主要疾病活动度指标和炎症指标之间未发现显著相关性。这一结果提示，miR-3960 可能更多地反映 RA 某些较为稳定的病理维度或慢性病程相关的背景性变化，而非短期或急性期炎症活动的波动。ROC 分析结果表明，miR-184-3p、miR-200a-3p、miR-133a-3p 和 miR-3960 对 RA 与健康对照组具有较高的诊断鉴别效能。其中，miR-184-3p 和 miR-133a-3p 在 RA 活动期与稳定期的区分中表现出较好的诊断效果。这些 miRNA 有望作为 RA 的潜在生物标志物，帮助疾病的早期诊断与监测。

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