·综　述·

机器学习在类风湿性关节炎诊疗及并发症预测中的研究进展

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［摘　要］ 类风湿性关节炎（rheumatoid arthritis，RA）作为一种慢性系统性自身免疫性疾病，以滑膜炎和进行性关节破坏为特征，具有高致残率与复杂并发症风险，严重威胁患者生活质量。尽管传统诊疗方案可以显著改善患者症状，但其早期诊断困难、治疗反应个体差异大及心血管疾病、间质性肺病等并发症的发生率高，仍是临床实践中的焦点问题。近年来人工智能与机器学习技术的快速发展，为突破RA诊疗瓶颈提供了全新机遇。通过深度挖掘RA多模态医学数据，如影像学、基因组学和电子健康记录等，机器学习模型在早期诊断、治疗反应分层管理及并发症风险建模，如心血管事件预警中均展现出潜在优势。但数据异质性、模型可解释性不足及临床转化障碍等问题仍制约其广泛应用。文章旨在系统梳理机器学习在RA诊疗中的最新研究进展，为RA依据机器学习技术实现精准诊疗提供理论依据与实践参考。

［关键词］ 机器学习；类风湿性关节炎；并发症；诊疗

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Machine learning in rheumatoid arthritis：advances in clinical diagnosis，treatment，and complication prediction

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［**Abstract**］ Rheumatoid arthritis（RA）is a chronic systemic autoimmune disease characterized by synovitis and progressive joint destruction，leading to a high disability rate and complex complications that severely compromise patients' quality of life. Although traditional diagnosis and treatment have been shown to significantly enhance patient symptoms，challenges such as the difficulty of early diagnosis，substantial individual variability in treatment response，and the high prevalence of complications，including cardiovascular diseases and interstitial lung disease，continue to be focal points in clinical practice. Recent rapid advancements in artificial intelligence and machine learning（ML）technologies offer novel opportunities to overcome these bottlenecks in RA management. By deeply mining RA multimodal medical data，such as patient imaging，genomics，and electronic health records，ML models have shown potential advantages in early diagnosis，stratified management of treatment response，and modeling of complication risk，such as early warning of cardiovascular events. However，barriers such as data heterogeneity，limited model interpretability，and challenges in clinical translation hinder its widespread adoption. This paper systematically reviews the latest research progress in applying ML to RA diagnosis and treatment，aiming to provide a theoretical foundation and practical reference for realizing ML-driven precision medicine in RA.

［**Key words**］ machine learning；rheumatoid arthritis；complications；diagnosis and treatment

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类风湿性关节炎（rheumatoid arthritis，RA）是一种慢性系统性自身免疫性疾病，在过去30年里，RA及其相关并发症发病率不断上升。有研究显示，2050年患者数将达到3亿[1]。其发病机制与多种炎症细胞浸润引起的关节缺氧和免疫失调密切相关[2]。RA

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引起的长期慢性骨骼、关节炎症可导致疼痛、关节畸形，严重可致滑膜组织失去功能[3]。目前主要采取抗风湿药的常规疗法来改善患者病情，最常使用的药物为甲氨蝶呤与糖皮质激素，它们能够抑制干扰素等致炎因子、诱导白介素（interleukin，IL）-10等抗炎因子的产生，但该类药物长期使用会出现明显的不良反应，如代谢紊乱、胃肠道溃疡和骨质疏松等，且该类药物仅能改善患者症状，难以根治RA[4]。现阶段RA的诊断主要依据患者临床表现、实验室检查以及影像学检查，但其早期症状无特异性[5-6]，常与骨关节炎等疾病混淆，现有指标也无法全面反映疾病严重程度以及伴发并发症的风险，同时由于人群异质性，不同患者对治疗药物的敏感度也存在明显差异[7-9]，亟待强化诊断体系以提高临床对RA的治疗效力。

近年来人工智能（artificial intelligence，AI）逐渐兴起，机器学习（machine learning，ML）作为AI的一个分支，是一种利用计算机系统整合已有数据进行自主学习与深度分析的技术。通过构建模型，ML可从现有数据中发现规律，从而对新数据进行预测或决策。由于ML能够处理复杂、高维的数据，并通过变量间的关联得出规律，因此被广泛应用于医疗领域进行疾病诊断、预测疾病进展和药物研发等[10]。

ML算法目前分为有监督、无监督、半监督和强化学习4种，监督学习通过标记数据进行训练，主要包括分类分析与回归分析，常见模型有支持向量机（support vector machine，SVM）、随机森林（random forest，RF）、最小绝对收缩和选择运算符（least absolute shrinkage and selection operator，LASSO）等；无监督学习对未标记数据进行处理，模型需要自己发现数据中的结构和模式，包括聚类、降维和特征学习；半监督学习兼具监督和无监督学习的特点，通过利用少量标记数据和大量未标记数据进行模型训练；强化学习通过与环境交互解决问题，通过不断试错进行纠正[11]。不同算法各具优势，因此要依据目的选择合适模型，当单一模型无法有效解决问题时，亦可采用混合模型达到最优效果。现阶段RA诊疗模型常依托监督学习模式，主要应用算法见表1。近年来，ML的快速发展，为RA诊疗提供了新的机遇与挑战，文章旨在系统梳理ML在RA及其并发症诊疗中的最新研究进展，为RA诊疗的智能决策提供理论依据与实践参考。

表1　RA诊疗常用算法汇总表

Table 1　Summary table of common algorithms for RA diagnosis and treatment

Algorithm type	Typical algorithms	Theory	Advantage	Disadvantage	Applicable scene
Linear model	Linear regression, logistic regression	Predicting output through feature linear combination (regression or classification)	Efficient computation, strong interpretability, and support for probabilistic output	Cannot automatically handle non-linear and be sensitive to outliers	Linear relationship problem (binary classification)
Support vector machine	SVM	Search for the hyperplane that maximizes the class separation, and the kernel function handles nonlinearity	High-dimensional data performs well and the kernel techniques are flexible	High computational complexity and parameter sensitivity	Medium - and small - sized high - dimensional data (text classification, image classification)
K-nearest neighbor	KNN	Predictions are made through majority voting or averaging based on neighboring samples	Simple and requiring no training or adaptation to local patterns	High computational complexity and sensitive to noise	Low-dimensional small data, with distinct local patterns
Ensemble learning	RF, XGBoost	Two strategies of random data sampling and random feature selection aggregate the results through voting or averaging	Random forest can resist overfitting and is highly parallelizable	The random forest may underfit simple data	Complex nonlinear tasks
Neural network	CNN, RNN, Transformer	Multilayer nonlinear transformation for learning feature representation	Strong ability in complex pattern modeling (for images and texts)	Requires a large amount of data and computing power	Unstructured data (image recognition)

1 影像学ML多模态数据赋能诊疗RA

ML结合影像学检测对RA的早期诊断有极高价值。未分化关节炎(undifferentiated arthritis,UA)有进展为RA的可能,预测其进展仍是临床难题。基于此,Hu等[12]对432例UA患者进行为期1年的随访,其中152例(35.2%)进展为RA,RF模型集成18个关节超声评分系统(ultrasound 18,US18)与临床基线数据,对该结果展现出极高的预测灵敏度和准确度,在此基础上,利用沙普利加性解释(Shapley additive explanations,SHAP)分析还找出关键变量,证实US18中2级关节计数、US18总分和肿胀关节计数对早期RA的检测至关重要。另一研究团队通过风湿病门诊招募符合入组条件的143例RA患者,将其随机分为训练集和验证集,放射科医生将训练集患者的临床数据、静态和动态超声影像结果依据欧洲抗风湿病联盟-风湿病评估量表(European Alliance of Associations for Rheumatology-Outcome Measures in Rheumatology,EULAR-OMERACT)、滑膜内血流情况(0~3分)和滑膜增生肥大(0~3分)进行赋分,用以构建卷积神经网络评分模型(ResNet50)进而评估验证集RA的活动度,最终模型评估结果与医生诊断保持一致,提示该模型有辅助放射科医生进行RA诊断的潜能[13]。

ML结合影像学检测也可监测RA并发症。骨质疏松症是RA患者最常见的关节并发症,为了找寻更快捷的评估工具,Saito等[14]尝试使用手部X线片计算第二掌皮质指数(second metacarpal cortical index,2MCI)预测骨密度(bone mineral density,BMD),最终成功结合临床指标构建出了具有高性能与高泛化能力预测RA患者骨质疏松的ML模型。间质性肺病(interstitial lung disease,ILD)是RA的关节以外并发症,McDermott等[15]使用定量计算机断层扫描(quantitative computed tomography,QCT)对RA患者及健康对照肺部数据利用多变量线性回归分析,发现RA与肺部较高的间质变化相关,且合并肺气肿的RA患者病死率远高于单纯RA患者。DAS-28评分是临床评价风湿活动性的传统指标[16],Zhou等[17]通过对RA患者28个关节评分(Disease Activity Score based on 28-joint count,DAS28)结合实验室检测指标等,构建的列线图模型则可用于RA患者并发ILD风险的预测,其中高龄、吸烟、DAS28评分升高、影像学关节分期较高(Ⅱ期和Ⅲ期)和甲氨蝶呤治疗等被确定为RA-ILD的独立危险因素。还有多项研究使用深度卷积神经网络(convolutional neural network,CNN)对十几万张胸部有异常的患者X线片进行分析,建立了名为DLAD-10(Deep-Learning Algorithm Detecting 10 Common Abnormalities)和CheXNeXt(Chest X-ray NeXt)的DL模型,可及时有效地辅助医生判断患者胸部的异常表现,同样有诊断RA-ILD的潜能[17-18]。

2 分子生物学ML多模态数据赋能诊疗RA

ML结合基因检测结果有效提高RA的诊断率。循环抗瓜氨酸肽抗体(anti-cyclic citrullinated peptide antibody,ACPA)是RA诊断的特异性指标,但很多患者早期的ACPA呈现阴性,这就使得RA诊断常出现延迟[19]。有研究收集173例RA患者外周血$CD4^+$ T细胞行基因芯片检测,以发病初期明确为RA的111份样本作为训练集构建出12基因诊断模型,该模型对于验证集ACPA阴性的RA患者的诊断灵敏度为0.85,特异度为0.75,提示基因测序数据的多基因特征模型有利于早期诊断RA[20]。类似地,一些研究利用基因表达公开数据集(gene expression omnibus,GEO)或收集样本的RA测序数据,使用加权基因相关网络分析(weighted gene co-expression network analysis,WGCNA)与LASSO、支持向量机递归特征消除(support vector machine recursive feature elimination,SVM-RFE)和RF算法等识别出滑膜中RRM2、DLGAP5、KIF11、AKR1C3、MCEE、POLE4和PFKM,$CD8^+$ T细胞中的GDF15、IGLC1、IGHM、CD8A、GZMA和PRF1,血小板细胞关联密切的MAPK3、ACTB、ACTG1、VAV2、PTPN6和ACTN1[21-25],滑膜趋化因子CXCL4与CXCL7均可作为RA早期发生的标志[26]。也有研究使用单细胞测序结果结合极端梯度提升(extreme gradient boosting,XGBoost)算法识别出RA中MIER1、PPP1CB、ICOS、GADD45A和CD3D这5个上调基因与$SLFN_5$、PIP4K2A和IL6ST这3个下调基因可以联合进行RA诊断[27]。一研究团队选取72例RA、8例UA和13例健康志愿者的外周血单个核细胞(peripheral blood mononuclear cell,PBMC)DNA样本进行甲基化测序,使用SVM算法构建UA向RA分化的DNA甲基化特征谱,进而监测UA进展[28],而Geng等[29]则通过合并GEO数据库RA滑膜组织的基因测序结果,共有233例RA和126例对照,通过构建LASSO模型找出了IGF2BP3和YTHDC2两个m6A甲基化调节因子,相比健康者,RA患者的IGF2BP3和YTHDC2显著升高。另一研究利

用公共数据库数据集对RA患者外泌体差异表达lncRNA使用SVM、KNN、RF和Logit算法进行DL，找出了DLEU2、FAM13A-AS1、MEG3和SNHG15这4种具有RA代表性的基因，它们有作为RA早期诊疗靶标的潜能[30]。针对代谢综合征相关RA（metabolic syndrome - rheumatoid arthritis，MetS - RA）患者，从GEO数据库中获得了3个RA数据集和1个MetS数据集，利用LASSO和RF识别出TYK2和TRAF2可作为MetS-RA的潜在标志物[31]。另外，使用ML整合患者临床数据可对患者的疼痛等级进行精确分类，从而帮助医生开展治疗[32]。也有研究基于图谱的基因表达模块鉴定（graph-based gene expression module identification，GbGMI）算法表明滑膜成纤维细胞中815个基因与疼痛有关[33]。前述研究均表明ML结合基因测序数据对RA的精准诊断和明确分级有潜在价值。

ML利用分子检测结果亦可辅助RA并发症的预判。有研究使用153例伴发ILD的RA和单纯RA患者静脉血标本，采取LASSO、RF、偏最小二乘回归（partial least squares regression，PLS）共同找出KL-6、D-二聚体和CA19-9可作为判断RA-ILD的潜在血液生物标志物[34]。无监督ML通过聚类分析显示，RA与精神/行为类或心血管类、慢性疼痛障碍类合并症相关性最高[35-36]，约15%的RA患者会出现抑郁症状，有研究使用LASSO结合SVM/RF算法对RA合并重度抑郁症患者的特异性差异表达基因构建模型，找出了AURKA、BTN3A2、CXCL10、ERAP2、MARCO、PLA2G7、EAF1、SDCBP和RNF19B作为潜在治疗靶点[37-38]。还有研究发现RA会加重动脉粥样硬化性心血管疾病，使用RF或递归神经网络（recurrent neural network，RNN）等算法可有效辅助判断RA患者并发心血管疾病的风险[39-40]。Feng等[41]使用LASSO、RF和逻辑回归（logistic regression，LR）交叉找出低密度脂蛋白（low-density lipoprotein，LDL）、调节性T细胞（regulatory T cell，Treg）占比和总胆固醇（total cholesterol，TC）水平是RA伴发心血管疾病的危险因素。LASSO与RF算法表明，NFIL3、EED、GRK2、MAP3K11、RMI1和TPST1[42]，还有9种miRNA（let-7c-5p、miR-30e-5p、miR-4446-3p、miR-126-5p、miR-3168、miR-425-5p、miR-126-3p、miR-30a-5p和miR-125a-5p）对RA伴动脉粥样硬化具有较高的诊断价值[43]。风湿症状可能伴随恶性肿瘤，为此Gente等[44]使用多变量Logistic回归分析，选取了4种代谢物浓度和1种脂质比值作为模型变量，构建出曲线下面积（area under curve，AUC）为0.995的RA诊断模型，其灵敏度与特异度也较高，可用于预测包括RA在内的约2/3的风湿性肌肉骨骼疾病（rheumatic musculoskeletal disorder，RMD）患者同期患有癌症的风险。

3 细胞标志物ML多模态数据赋能诊疗RA

ML结合不同种类细胞相关标志物可进一步辅助诊断RA。有研究报道细胞铁死亡、铜死亡等可加重RA的病理过程，通过GEO数据库中RA数据集的差异基因与844个铁死亡相关基因取交集，LASSO分析交集基因发现MMP13升高与GABARAPL1降低可作为RA的标志[45]。类似地，铜死亡相关基因SLC35A1、PRPF39、MAP4K3、TMX1和FAM96A具有潜在的诊断价值，可用于预测RA患者的病理结局[46]。乳酸化作用在免疫细胞代谢及基因表达改变中具有重要调节作用，Fu等[47]采用134种ML算法组合对RA基因测序结果进行训练，找出7个核心促乳酸化相关基因，该诊断模型AUC可达0.918，qRT-PCR证实NDUFB3、NGLY1和SLC25A4在RA中高表达。为研究乳酸代谢与RA的关系，Yang等[48]使用类似方法找到与巨噬细胞功能相关的KCNN4和SLC25A4以及参与树突状细胞免疫的GATA2基因，它们均有望成为RA治疗靶点。Adami等[49]从骨代谢角度出发，使用主成分分析（principal component analysis，PCA）方法发现骨中较低的PINP和B-ALP可有效诊断RA。另外，根据血清傅里叶变换红外光谱和DL算法构建的MSResNet模型也具有良好区分强直性脊柱炎（ankylosing spondylitis，AS）、骨关节炎（osteoarthritis，OA）和RA患者的性能[50]。以上均说明ML结合与RA密切相关的细胞标志物亦有提高临床RA诊断能力的潜在价值。

4 ML能预测RA药物疗效

推动精确医学、提高药物疗效是治疗RA的关键[51]。Li等[52]收集了56例甲氨蝶呤治疗失败（methotrexate-inadequate response，MTX-IR）并计划采用肿瘤坏死因子抑制剂（tumor necrosis factor interference，TNFi）治疗的RA患者的血浆外泌体，对其基因测序结果使用RF和LASSO回归各自产生核心基因后作交集，并最终确定has-circ0002715与has-circ0001946为关键基因，可用于预测MTX-IR RA患者及作为开启TNFi治疗的标志物。并且，监测MTX治疗前后4周内的基因变化也有助于判断患者是否

适合MTX治疗[53]。同时,MTX-IR还与高淋巴细胞计数有关,淋巴细胞计数高于2 000个/mL的患者,MTX治疗更易失败[54]。Zhang等[55]开发出新型纳米级材料运载药物至发病部位进行释放,提高了药物治疗RA的精准度,减少了药物不良反应,同时结合自适应神经元模糊推理系统(adaptive neuron fuzzy inference system,ANFIS)和XGBoost ML模型可预测该方式药物的治疗效能。还有研究围绕治疗RA的一种中药白花蛇舌草,利用网络药理学和生物信息学展开分析,最终通过LASSO、RF和SVM-RFE算法及分子对接确认MMP9为该药物治疗RA的核心靶点[56]。Ye等[57]利用7年间的RA患者就诊数据及就诊时气象因素和空气污染,利用长短期记忆(long short-term memory,LSTM)模型有效预测RA患者就诊情况,有利于优化医疗资源分配。

约40%的RA患者对特定药物治疗无反应,使用ML可针对性地给予不同患者个性化的用药建议[58-59]。Rivellese等[60]使用利妥昔单抗以及托珠单抗治疗的RA患者滑膜组织行RNA测序,利用10×10倍嵌套交叉验证方法结合测序结果详细找出了与利妥昔单抗相关的40个基因和与托珠单抗相关的39个基因,其预测药物有效性的准确度分别达0.744和0.681。Ukalovic等[61]依托患者临床数据利用交叉验证方法开发5种RA生物特定疾病修饰药物(disease-modifying drug,DMARD)的疗效预测模型,发现阿达木单抗(adalimumab,ADA)和依那西普(etanercept,ETN)联用治疗效能最高。对RA患者外周血$CD4^+$ T细胞进行RNA测序及DNA甲基化测序,利用XGBoost和RF算法依据差异基因和差异甲基化位点(differentially methylated position,DMP)训练出的模型可有效预测患者对ADA和ETN的治疗反应,相比药物治疗无效者,有疗效的患者呈现基因高甲基化状态,其准确率分别达84.7%和88.0%[62-63]。类似地,使用SVM算法开发出的结合临床基线数据和外周血7种DMP评分的预后模型可用于判断患者对来氟米特治疗是否敏感[64]。有研究整合了RA外周血基因的转录组图谱,并对外周血中404个上调的差异表达基因(differentially expressed gene,DEG)进行功能富集分析,使用ML中的无监督聚类分析确定3种最佳分类亚型,分别为中性粒细胞驱动、干扰素驱动和$CD8^+$ T细胞驱动,有助于针对RA的个性化给药[65]。Baxter等[66]使用XGBoost结合5 481例患者临床监测数据训练出判断RA患者5年接受手术的概率(AUC=0.90±0.02)以及接受关节置换还是其他手术(AUC=0.58±0.10)的模型,以期实现对RA患者的精准治疗。

RA除可造成关节与器官损伤外,还会伴随其他多系统临床症状。RA易造成严重感染(serious infection,SI),Hetland等[67]通过统计学结合ML技术对8 404例使用托法替布治疗的RA患者数据进行分析,进一步证实了年龄较大、男性、既往感染史和基线时皮质类固醇使用与SI风险密切相关,而Mehta等[68]则是使用LASSO分析得出,相比非炎性风湿及肌肉骨骼疾病,RA患者SI风险显著增加。

5　总结与展望

随着ML的逐步推广,医学领域也开始不断尝试融合这种先进方法以寻找各类疾病相关的靶向基因、通路和生物标志物等,进而发现潜在诊疗靶点及治疗途径。目前已开发出大量RA相关的ML模型(表2),这些模型的构建为参与测试的患者提供了病情分类、基因差异分析、生存期预估相关的结果,有助于患者清晰了解自身状况,为患者的治疗与预后提供了新方向,且ML可以有效地将影像、血液检测和基因检测,如临床基础数据、关节评分、免疫细胞计数、特异性抗体检测、核酸标志物检测等多维度数据进行整合分析,高精准度、低错误率地迅速产生诊断建议,辅助临床医生高效诊疗RA,具有潜在应用价值(图1)。但其应用于临床实际仍存在较大困难,挑战之一是如何有效融合多模态数据,依据《中国类风湿关节炎发展报告2020》[69],RA的诊断标准主要包括患者伴有晨僵等临床症状,手部X线检查显示骨质疏松以及血清类风湿因子水平升高等,这些数据检测手段不同,结果差异大,现有的算法进行融合分析仍存在技术困难。再者若想将所建立的模型直接应用于临床疾病诊断,则需要把所开发的算法模型嵌入现有的如影像、检验等大型仪器中,这就需要提高仪器之间的信息互传以及数据兼容性,目前这一工作难度较高,且伴随科技飞速发展,RA诊断模型的开发愈来愈全面和深入,实时数据更新和系统维护也将成为重点和难点。且ML训练模型需要依赖大量原始数据,但当前许多研究中使用的样本量偏少,尽管研究者们会通过采取交叉验证、特征降维等方式来对模型进行复查以获得较高准确率,但仍无法完全弥补因数据量过少所引起的模型不确定性,无法实现推广,导致投入临床使用的模型较少,更多仅是停留在实验室研究测试层面。为了提高模型的质量、通用性和可用

性，后续则需要纳入更多数据并进行多中心验证。

即使基于ML诊疗RA仍存在诸多风险与挑战，但其依然具有一定的意义和价值，持续优化ML搭建诊疗RA的可推广、可持续性模型具有提高RA患者早期诊断率以及改善预后的潜能。如哈佛大学研究团队开发了一款临床组织病理学成像评估基础模型，已在全球多家医院验证了其对肿瘤标本的诊断准确性，预计在2~3年内推出商业化工具[70]；另外北京邮电大学科研团队通过多种医学数据和综合评估微调构建的大型语言模型ClinicalGPT，在训

表2 ML赋能诊断RA及其并发症

Table 2 ML empowers diagnosis of RA and its complications

Algorithm	Modeling indicator	Reference
ML diagnosis of RA		
RF	Ultrasound scoring system -US18 Clinical baseline data	[12]
ResNet50	Clinical and ultrasound scoring system -EULAR-OMERACT Clinical blood flow within the synovium（0-3） Synovial tissue hyperplasia and hypertrophy（0-3）	[13]
SVM，LASSO	Clinical baseline data QCT pulmonary scan	[15]
RF，SVM	Clinical baseline data Joint characteristics：joint deformity，tender joint count，swollen joint count，DAS28 score，joint function，and joint radiological staging laboratory indicators：circulating anti-citrullinated peptide antibodies，etc. Treatment situation：methotrexate，hormone therapy，etc.	[17]
DCNN	Chest X-ray image	[18]
SVM	Combined detection of RA characteristic genes for $CD4^+$ T cells：LOC731186，CR748316，LDHA，IGFL2，CMAH，MUC1，PDCD1，PIM1，SOCS3，$SBNO_2$，BCL3，and NOG	[20]
WGCNA，LASSO，SVM-RFE RF	Combined detection of RA characteristic genes for $CD8^+$ T cells：GDF15，IGLC1，IGHM，CD8A，GZMA，and PRF1	[23-24]
XGBoost	Combined detection of RA characteristic genes for T cells：MIER1，PPP1CB，ICOS，GADD45A，CD3D，$SLFN_5$，PIP4K2A，and IL6ST	[27]
LASSO	Combined detection of RA characteristic genes for platelet：MAPK3，ACTB，ACTG1，VAV2，PTPN6，and ACTN1	[25]
LASSO	m6A methylation regulatory factors：IGF2BP3 and YTHDC2	[29]
SVM，KNN，RF，Logit	Serum exosomes LncRNAs：DLEU2，FAM13A-AS1，MEG3，and SNHG15	[30]
GLMVQ	Synovial chemokines：CXCL4 and CXCL7	[26]
WGCNA，LASSO，SVM-RFE RF	Synovial genes：RRM2，DLGAP5，KIF11，AKR1C3，MCEE，POLE4，and PFKM	[33]
RF，LASSO，PLS	Clinical baseline data Blood tests：blood cell count，erythrocyte sedimentation rate，C-reactive protein，immunoglobulin，lactate dehydrogenase，hydroxybutyrate dehydrogenase，KL-6，D-dimer，fibrinogen，fibrin degradation products，etc. Tumor markers include carbohydrate antigens（CA19-9，CA242）and carcinoembryonic antigen（CEA）	[34]
LASSO，SVM	Genetic testing for depression in patients with RA：AURKA，BTN3A2，CXCL10，ERAP2，MARCO，PLA2G7，EAF1，SDCBP，and RNF19B	[37]
LASSO，RF，LR	Laboratory tests：blood cell count，number of immune cells，lipoproteins，cholesterol，etc.	[41]
RF，ENR	Genetic testing for rheumatoid arthritis with atherosclerosis：let-7c-5p，miR-30e-5p，miR-4446-3p，miR-126-5p，miR-3168，miR-425-5p，miR-126-3p，miR-30a-5p and miR-125a-5p	[43]
Monitoring the efficacy of drugs using ML		
RF，LASSO	Serum exosomes：has-circ0002715 and has-circ0001946	[52]
LSTM	Determine the patient visit rate：meteorological factors，air pollutants，and patient historical visit data	[57]

（续表2）

Algorithm	Modeling indicator	Reference
Ten-by-tenfold nested cross-validation	Rituximab-related 40 genes：SHC3，XCR1，TCN1，DLX4，PLEKHG，etc. Tocilizumab-related 39 genes：SHC3，XCR1，DLX4，MYH6，TCN1，etc.	[60]
Cross-validation	Clinical baseline data for monitoring the efficacy of drug treatment	[61]
XGBoost，RF	DNA methylation sequencing of peripheral blood $CD4^+$ T cells after drug treatment	[63]
SVM	Clinical baseline data on the effectiveness of leflunomide treatment The efficacy of leflunomide treatment on peripheral blood differential DNA methylation sites：cg17330251，cg19814518，cg20124410，cg21109666，cg22572476，cg23403192，and cg24432675	[64]
XGBoost	Whether RA will undergo surgery：patient's clinical baseline data	[66]

RF：random forest；CNN：convolutional neural network；DCNN：deep convolutional neural network；ANN：artificial neural network；Bi-LSTM：bidirectional long short term memory；AM：additive model；SVM：support vector machine；SVM-RFE：support vector machine recursive feature elimination；SVM-RBF：support vector machine radial basis function；LASSO：least absolute shrinkage and selection operator；LSTM：long short term memory；MSResNet：multiscale residual network；GBT：gradient boosting decision tree；SSGB：stability selection gradient boosting；LGBM：light gradient boosting machine；XGBoost：eXtreme gradient boosting；glmBoost：generalized linear model boost；GMM：gaussian mixture model；ANFIS：adaptive neuron fuzzy inference system；RC：ridge regression；ENR：elastic net regression；KNN：K nearest neighbor；PLS：partial least squares regression；CC：consensus cluster plus；DEC：deep embedded cluster；LR：logistic regression；MA：multivariate analysis；MLR：multiple linear regression；SFS：sequential forward selection.

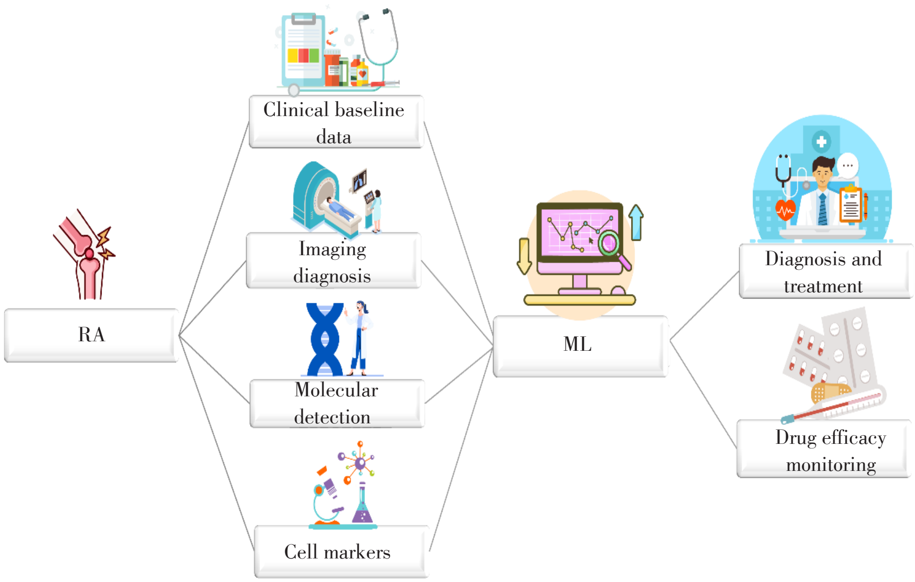

图1　ML辅助RA诊疗流程图（Office Plus绘制）

Figure 1　ML assisted RA diagnosis and treatment process diagram（drawn by Office Plus）

练过程中融入广泛且多样化的现实世界数据，如病历、特定领域知识和多轮对话咨询，通过医学知识问答、医疗检查、患者咨询和病历诊断分析等进行多维度验证，其诊断能力均显著优于其他模型[71]。虽然前述模型并未特别针对RA诊疗，但模型构建机制对于开发RA诊疗模型有很高的借鉴价值。

现阶段还需突破ML对于不同维度数据的整合分析能力，伴随AI，例如DeepSeek等相关大模型的开发，大幅提高了对不同数据的整合能力，并呈现数据处理过程的详细解析。同时这种诊断模型是整个医院甚至整个社会公用的，这也就需要全社会建立公认算法，并加强对医护人员的持续培训。最后，加强多中心交互实践，汇集多家医院、诊疗中心以及实验室的检测数据进行整合分析，建立可推广、普适性的诊疗模型，同期构建诊疗模型监管网络，杜绝人为篡改或擅用医疗数据，以便真正助力诊疗，服务患者。

利益冲突声明：

所有作者声明无利益冲突。

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YAN Shutong was responsible for literature search，initial draft writing of paper; LIU Qi was responsible for topic selection guidance，paper inspection，review and revision.

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