Advances in Clinical Medicine 临床医学进展, 2025, 15(6), 1480-1487
Published Online June 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1561876

Hans汉斯

基于定量CT评估CTD-ILD的研究进展

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收稿日期：2025年5月23日；录用日期：2025年6月16日；发布日期：2025年6月25日

摘　要

间质性肺疾病(ILD)是结缔组织病(CTD)患者常见的并发症和死亡的主要原因。CTD的复杂性给结缔组织病相关间质性肺疾病(CTD-ILD)的诊断与治疗带来了重大挑战，而定量CT在CTD-ILD的诊断、分型、严重程度评估及预后方面展现出潜在应用价值。本文将半定量及定量CT在CTD-ILD中的应用与挑战进行综述，强调定量CT对实现CTD-ILD精准分型、严重程度评估及风险预测的重要性，并对未来研究方向予以展望。

关键词

结缔组织病，间质性肺疾病，HRCT，定量CT

Research Progress in Evaluating CTD-ILD Based on Quantitative CT

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Received: May 23rd, 2025; accepted: Jun. 16th, 2025; published: Jun. 25th, 2025

Abstract

Interstitial lung disease (ILD) is a common complication and a major cause of death in patients with connective tissue disease (CTD). The complexity of CTD poses a major challenge in the diagnosis and treatment of connective tissue disease-associated interstitial lung disease (CTD-ILD), and quantitative CT has demonstrated potential applications in the diagnosis, staging, severity assessment and prognosis of CTD-ILD. In this article, we review the applications and challenges of semi-quantitative and quantitative CT in CTD-ILD, emphasise the importance of quantitative CT in achieving accurate typing, severity assessment and risk prediction of CTD-ILD, and provide an outlook on future research directions.

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文章引用: 王珂, 冀韩英, 黄晓旗. 基于定量 CT 评估 CTD-ILD 的研究进展[J]. 临床医学进展, 2025, 15(6): 1480-1487.
DOI: 10.12677/acm.2025.1561876

Keywords

Connective Tissue Disease, Interstitial Lung Disease, HRCT, Quantitative CT

1. 引言

结缔组织病(connective tissue disease, CTD)是一组涵盖类风湿性关节炎、系统性红斑狼疮、系统性硬化症等自身免疫性疾病的统称[1]。而间质性肺疾病(Interstitial Lung Disease, ILD)是 CTD 常见的并发症[2]和死亡的主要原因[3]。一旦 ILD 病情进展，预后通常不佳[4]。因此，早期识别并干预 CTD 患者的肺部间质性改变对于延缓病情进展至关重要。

CTD 的复杂性使 CTD-ILD 的诊断和治疗面临重要挑战。尽管肺活检被视为金标准，但由于其侵入性而导致应用受限[5]。虽然 HRCT 和肺功能为常用筛查方式[6]，但肺功能对早期病变敏感性不足且重度患者难以配合[7]，所以，目前认为 HRCT 是 CTD-ILD 的主要诊断工具[8]。而定量 CT 以客观性和重复性优势在 ILD 的诊断及病情评估中展现出潜在应用价值[9]。本文将介绍常见的 CTD-ILD 的半定量及定量 CT 评估方法，并探讨其在疾病诊断、分型、严重程度评估以及预后中的应用价值，为无法接受肺功能检查的患者提供非侵入性评估方式。

2. 半定量 CT 方法

目前主要采用三种评分系统来评估间质性肺疾病(ILD)的严重程度。

2.1. Goh 评分

Goh 评分[10]在五个特定的肺部层面(大血管起源处、主气道分叉处、肺静脉汇合处、第三节与第五节之间的中点、以及紧邻右侧膈肌上方)估计 CT 图像 ILD 病变范围占该层面总面积的百分比，精确到5%，五个层面的平均值为 ILD 的总范围，依据 ILD 总范围分为局限性(<20%)和弥漫性(>20%)两组，对于不确定的病例，则参考用力肺活量百分比(predicted forced vital capacity, FVC%)的 70%阈值进一步划分。该评分操作简便，已有研究证实与定量 CT 指标[11] (如峰度、偏度、平均肺衰减值)及肺功能指标[12] (FVC%、FEV1%、TLC%和 DLCO%)等有良好的相关性，并且能提供患者的预后信息[10] [13]，即弥漫性患者具有更高的死亡风险。

2.2. Warrick 评分

与 Goh 评分不同，Warrick 评分[14]则详细量化了 CT 上各种肺部异常表现，包括磨玻璃样变、蜂窝状改变和胸膜下囊泡等，并结合受影响支气管肺段，将患者分为正常、轻度、中度和重度四个等级。Warrick 评分在 ILD 的严重程度评估方面具有显著优势，其全面性使得评分能够较准确地反映患者的病情。该评分与肺功能指标，如肺总量(total lung capacity, TLC%)和一氧化碳弥散量(predicted diffusing capacity of the lung for carbon monoxide, DLCO%)等，存在良好的相关性[15]。更重要的是，对于系统性硬化症(Systemic Sclerosis, SSc)患者而言，Warrick 严重程度评分不仅与诱导皮肤和肺纤维化的 IL-13 水平显著相关[16]，还与食管疾病受累存在紧密的关联[17]。这一发现不仅揭示了 SSc 病理生理过程中的一些重要机制，还为制定更有效的治疗方案提供了重要依据。

2.3. Kazerooni 评分

Kazerooni 评分[18]则选取上、中、下肺叶的代表层面计算五个肺叶的平均分数，分别得出磨玻璃影和纤维化的评分。研究表明，该评分与密度直方图在 ILD 的病情评估中显示出良好的操作者间一致性[19]，并且纤维化评分与 DLCO 呈负相关[19]。此外，磨玻璃评分与独立关联于类风湿性关节炎相关间质性肺疾病(Rheumatoid Arthritis-Interstitial Lung Disease, RA-ILD)严重程度的唯一血清标志物(IgA RF)的水平呈显著正相关[20]。

对比三种评分发现，Goh 评分具有良好的评估者间一致性[21]。目前，Warrick 和 Goh 评分系统在视觉评估中占据了主导地位，成为最常用的两种评分方法[22]。虽然 CT 视觉半定量评分高度依赖医生主观判断，存在观察者内和观察者间变异，且可重复性低，难以精确捕捉病变细微特征及短期变化，但其简便易行、易于推广，是评估 ILD 严重程度不可或缺的重要参考工具，为疾病的病情监测及疗效评估提供了一定的影像学支持。

3. 定量 CT 方法

通过专用的软件对肺组织进行自动分割，得到相应的定量指标。目前常用的定量方法主要有密度直方图法、密度阈值法、纹理分析法、影像组学等。

3.1. 密度直方图法

密度直方图法是通过统计 ILD 患者 HRCT 图像中不同密度范围内的像素数量或比例，提取多种量化指标，包括峰度、偏度、平均肺衰减值、高密度衰减等。峰度可反映肺部组织密度的集中或分散状态，当峰度异常高时，预示着肺部存在显著的纤维化区域。偏度则提示肺密度分布是否偏向高密度或低密度区域，它有助于识别纤维化或肺气肿等病理改变。而标准差数值较高通常表明肺组织密度存在显著差异，可能与 ILD 的严重程度或分布范围密切相关。高密度衰减定义为衰减在−600 到−250 HU 之间的体素的百分比[23]，主要代表磨玻璃影和网格影，这在 ILD 中很常见，对 ILD 的诊断和评估具有重要意义。

多项研究已经证实了密度直方图法在 ILD 评估中的有效性。如，Gaetano 等发现[19]特发性纤维化患者肺平均衰减可用来预测患者肺功能的恶化。使用平均肺衰减、偏度和峰度不仅能评估干燥综合征相关间质性肺疾病(Sjogren syndrome-Interstitial Lung Disease, SS-ILD)患者疾病严重程度[11]，并且合并后的计算机综合指数(Computerized composite index, CII)还能显著预测 SSc-ILD 患者的死亡率[24]。高密度衰减与间质性肺疾病(ILD)的纤维化严重程度密切相关，是 ILD 纤维化的最佳单一指标[25]，能有效识别出有 ILD 风险但无症状的 RA 患者[26]，从而指导筛查。Bina Choi 等人的研究[27]也进一步验证了高密度衰减作为亚临床 ILD 有效量度的可行性。

尽管密度直方图能够反映 ILD 患者的整体 CT 密度分布，但它无法提供关于病灶空间分布的具体信息，这限制了其在评估 ILD 病情严重程度和分布特征的能力。此外，不同的 CT 重建算法可能会对 ILD 的定量评估产生影响，从而导致密度直方图的结果在不同条件下存在差异，这增加了结果的不确定性和解释难度。

3.2. 密度阈值法

密度阈值法是通过设定特定的密度阈值，将 ILD 患者 HRCT 图像的像素分为不同的类别(如正常肺组织、纤维化区域等)，并计算各类别像素的数量或比例来评估 ILD 的严重程度。

密度阈值法得到的 ILD%与 Warrick 评分和肺功能之间存在显著关联[15]，验证了其评估 ILD 严重程度的准确性和可靠性。更重要的是，它还能有效区分特发性炎症性肌病中抗氨酰转移 RNA-合成酶阴性和

阳性的患者[15]，为临床诊断和治疗提供了更为精确的信息。而以磨玻璃密度、实变、网状和蜂窝影的总来定义的间质性肺炎总范围，被证实是进行性间质性肺疾病患者肺活量(VC)降低的重要指标[28]，这一发现对于那些无法进行肺功能检查的患者而言尤为重要，它提供了一种非侵入性的手段来预测肺功能的恶化趋势，有助于医生及时采取干预措施，延缓疾病进展。

但是，目前对 ILD 的阈值范围存在争议，这主要源于多个因素：首先，不同 CT 扫描设备和定量软件[29]-[32]在成像原理和数据处理上存在差异导致阈值设定不一致。例如，一些文献报道的阈值范围为−200~−700 HU [29]、而有的研究则提出为−500~−700 HU [30]或−700~+99 HU [33]。因此，可研究不同设备和软件之间的差异，并尝试建立统一的校准标准。同时，结合其他定量 CT 方法(如纹理分析法)来综合评估肺部病变。此外，评估标准的多样性也是导致阈值差异的一个重要因素。不同的研究可能采用不同的评估标准来判定 ILD 的严重程度，如视觉半定量评分[12]、肺功能指标[34]等。这些评估标准与密度阈值之间的相关性也可能存在差异，从而导致阈值设定的不一致性。后续可引入一致性评估方法。其次，CTD-ILD 的病理和临床异质性，也是导致阈值差异的重要原因[35]。由于 CTD-ILD 患者的肺部病变类型和程度各不相同，所以在 CT 扫描上的密度特征也各异。这使得难以确定一个统一的阈值来准确评估所有患者的 ILD 严重程度。因此，可针对不同的 CTD 疾病类型或不同的影像类型设定阈值范围。

密度阈值法主要基于 CT 值进行分割，但无法考虑肺部病灶的形态学特征或局部空间关系，这限制了其在区分具有相似 CT 值的不同肺部病灶的能力。且该方法的分割结果容易受到其他因素(如肿瘤、感染等)的干扰，导致分割不准确或误导性的诊断。未来研究需综合考虑扫描仪和定量软件的差异、CTD-ILD 的病理和临床表现异质性以及评估标准的多样性等因素，以建立统一、可靠的诊断阈值标准。

3.3. 纹理分析法

纹理分析法利用特定算法提取和分析 CT 图像中的灰度值、空间分布、形状及方向等纹理特征，从而自动识别并分割出多种肺部异常区域，如肺气肿、磨玻璃影、实变、网状混浊和蜂窝状囊肿等。

纹理分析在 CTD-ILD 患者疾病严重程度评估和治疗反应方面比 Warrick 视觉评分更具潜力[36]。常用的纹理分析软件是美国梅奥中心研究开发的 CALIPER 软件，使用 CALIPER 评估 SSc-ILD，Ferrazzad 等人[37]发现磨玻璃影百分比是预测 DLCO 恶化的最佳指标(AUC = 0.75, p = 0.009)，但 Occhipinti 等人发现[38]定量 CT 指标预测疾病进展不准确，但可准确预测 FVC%和 DLco%复合功能呼吸终点(用于评估 SSc-ILD 患者疾病进展或改善的综合指标) (AUC = 0.74)，而 Amorim 等人[39]发现基线定量 CT 较高的网状模式是患者死亡率的独立预测因素(OR = 2.70, 95% CI 1.26~5.82)。值得关注的是，Ahn 等人[40]通过纹理分析计算 CTD-ILD 患者随访与基线磨玻璃影、实变、网状影和蜂窝影的体积百分比差值，结果表明 4%为进行性肺纤维化(Progressive pulmonary fibrosis, PPF)的最佳定量 CT 阈值，即百分比差值 ≥ 4%时存在放射学进展，这拓宽了纹理分析在 CTD-ILD 领域的应用范围。基于纹理分析对 CT 偶然发现的间质性肺异常也具有高灵敏度和特异性[41] [42]，这有助于实现 CTD-ILD 的早期诊断。

相比传统的密度阈值法，纹理分析法不易受图像噪声和伪影干扰，能提供更详细的肺部异常区域信息，提高了诊断的精确度和全面性。此外，纹理分析法还能反映疾病的进展和变化，为疾病的预后提供重要信息。因此，未来纹理分析在间质性肺疾病的 CT 评估领域可能是更有前景的研究方向[43]。

3.4. 影像组学与机器学习

影像组学和机器学习(machine learning, ML)在 CTD-ILD 的定量 CT 分析中是极具潜力的领域。影像组学能够将数字医学影像转化为高维数据，提取包括形状特征、纹理特征、衰减或强度分布特征等定量信息[44]。机器学习则通过计算机算法识别模型，包括监督学习和无监督学习两类。监督学习包括朴素贝

叶斯、逻辑回归、K 最近邻、随机森林、决策树、梯度提升树、支持向量机和多层感知器等模型，经过标记数据后进行预测；而无监督学习则在未标记数据中寻找预测模型。深度学习(deep learning, DL)是机器学习的分支，如卷积神经网络(convolutional neural networks, CNNs)等，通过多层处理单元进行特征提取和分类，避免手动提取特征，提高处理效率和准确性。

对于 CTD-ILD 这一复杂疾病而言，不同类型的 ILD 预后存在显著差异[45]，因此应针对不同病理分型和不同疾病类型具体研究。而 ILD 的 HRCT 影像模式与病理学结果密切相关[46]，通过影像组学和深度学习算法[47]，自动检测和分类 ILD 及其亚型，成功实现了对各类典型影像模式的精准临床分类，而结合定量 CT 与临床数据的 ML 模型[45]，在诊断准确性及组织病理学分类方面更是表现出色。由于 ILD 的非特异性和重叠的临床和放射学特征，仍有 10%~20%的 ILD 患者被归类为无法分类的 ILD [48]。为克服这一局限性，Haga 等人[49]将 CT 影像组学特征与外科肺活检的组织学标本比较，开发了评估 ILD 患者的细胞浸润预测模型，该模型通过分析手术肺活检标本，量化单位面积的有核细胞数量来评估细胞浸润程度。高细胞浸润可能需采取抗炎措施，且不同疾病类型的细胞浸润差异有助于鉴别诊断。这一创新有望提升定量 CT 分析在 ILD 分型中的准确性，为 ILD 的精准诊疗提供新视角。研究发现，被算法判定为 UIP 阳性患者的 FVC 年下降幅度显著高于 UIP 阴性者[50]，这证实了精确分类可预测患者肺功能下降趋势，以便早期干预以延缓肺纤维化进展。值得一提的是，一款基于计算机深度学习分析软件[51]在区分 FVC% < 70 患者方面表现优异，为肺功能评估和疾病预测提供了有力工具。此外，深度学习卷积神经网络模型在量化 ILD 类型、分期及识别普通型间质性肺炎(Usual interstitial pneumonia, UIP)方面表现出色[52]，而 UIP 作为 SSc-ILD 的重要预后指标，与其疾病进展及不良生存率密切相关[53]，这一技术的应用为 SSc-ILD 患者的预后评估提供了重要参考标准。

随着影像组学和深度学习技术的不断发展，CTD-ILD 的诊断、分型和预后评估将变得更加精准和高效，然而，目前该领域的研究数据有限，需要更多的数据和深入研究来进一步优化模型性能并验证其临床应用价值。

4. 总结和展望

综上所述，CTD-ILD 的定量 CT 研究领域正处于快速发展阶段，但仍面临诸多挑战和争议。未来需要建立统一、可靠的诊断阈值标准，开发更加先进的图像分割和识别算法，以克服当前技术的局限性。同时，应深入探究疾病病理生理机制与分子生物标志物，结合多学科知识实现对 ILD 患者的精准分型和诊断，以便医生制定个性化治疗方案，提升患者疗效并改善生活质量。此外，还应加强跨学科合作与交流，共同推动 CTD-ILD 领域的进步与发展。

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