



· 综述 ·

代谢相关脂肪性肝病的影像学无创评估研究进展

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[摘要] 代谢相关脂肪性肝病 (metabolic dysfunction-associated fatty liver disease, MAFLD), 原称非酒精性脂肪性肝病 (non-alcoholic fatty liver disease, NAFLD), 是现今临床最常见的非传染性慢性肝病, 若不进行有效治疗, 则可能进展为肝硬化, 甚至肝癌。早期诊断、早期干预MAFLD有助于延缓其发展, 逆转其病程。穿刺活检是MAFLD分期的金标准, 但是有创, 存在出血可能。无创评估MAFLD对于疾病的分期和干预治疗至关重要。为此, 本文回顾各类无创影像学技术在MAFLD诊断中的应用进展, 并分析其优缺点。

[关键词] 代谢相关脂肪性肝病; 非酒精性脂肪性肝病; 计算机体层成像; 磁共振成像; 超声

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The progress of no-invasive imaging assessment of metabolic dysfunction-associated fatty liver disease

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[Abstract] Metabolic dysfunction-associated fatty liver disease (MAFLD), also known as non-alcoholic fatty liver disease (NAFLD), is the most common noninfectious chronic liver disease at present. It will progress to liver cirrhosis and even hepatocellular carcinoma without effective treatment. Making diagnosis of MAFLD at the early stage is important for optimizing treatment plan and prevent progression. Liver biopsy is considered as the gold standard for the diagnosis and grading of MAFLD. However, it can be invasive and may cause bleeding during the procedure. Thus, it is necessary to find out more convenient and noninvasive methods to establish MAFLD severity. Here we reviewed and summarized the latest imaging techniques in the diagnosis of MAFLD.

[Keywords] Metabolic dysfunction-associated fatty liver disease; Non-alcoholic fatty liver disease; Computed tomography; Magnetic resonance imaging; Ultrasound

代谢相关脂肪性肝病 (metabolic dysfunction-associated fatty liver disease, MAFLD), 曾被称为非酒精性脂肪性肝病 (non-alcoholic fatty liver disease, NAFLD), 是由遗传易感和营养过剩及其并发症等导致甘油三酯在肝脏内过度沉积的常见脂肪性肝病, 疾病谱包括非酒精性单纯性脂肪肝 (non-alcoholic fatty liver, NAFL)、非酒精性脂肪性肝炎 (non-alcoholic steatohepatitis,

NASH) 及其相关的肝纤维化、肝硬化及肝细胞癌 (hepatocellular carcinoma, HCC) 等一系列病变^[1-2]。随着生活水平提高、代谢障碍及肥胖症的流行, MAFLD的发病率逐年上升。据报道, 全球范围内成人MAFLD发病率高达25.2%^[3], 2018年中国范围发病率为29.2%^[4], 已取代病毒性肝炎成为中国发病率最高的慢性肝病^[5]。MAFLD与心血管系统疾病、代谢性

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疾病以及肝外恶性肿瘤的发生、发展密切相关^[6]。早期诊断、早期干预MAFLD,可有效地逆转肝脂肪变性、肝炎及肝纤维化。肝穿刺活检作为MAFLD诊断的金标准存在患者接受程度低、费用高,以及易发生出血、胆漏、感染等潜在并发症的问题,对于不均匀性脂肪肝,由于取样标本局限,不能很好地评估肝脏整体的脂肪变性状态。影像学检查技术因其无创性,在MAFLD的早期筛查、评估及预后中的作用尤为重要。本文就MAFLD的影像学无创评估研究进展进行综述。

1 计算机断层成像 (computed tomography, CT)

1.1 常规CT

通常采用肝、脾CT值、肝脾CT比值(L/S)及肝血管的相对密度进行MAFLD的诊断。当脂肪浸润时,肝组织密度减低,肝脏CT值<40 HU、肝脾CT值差值<10 HU以及L/S<0.9可诊断为中度以上的脂肪肝^[7],其灵敏度为46%~72%,特异度为88%~95%^[8]。Pamilo等^[9]研究表明,肝脂肪变性患者的肝CT值在6~60 HU之间变化,轻度脂肪肝组的CT值为39~60 HU,中度脂肪肝组的CT值为4~46 HU,重度脂肪肝组的CT值为6~16 HU,由此可见不同程度的脂肪肝其CT值有一定的重叠,影响诊断的准确度。《中国非酒精性脂肪性肝病诊疗指南(2010年修订版)》^[10]规定轻度脂肪肝L/S为0.7~1.0,中度脂肪肝L/S为0.7~0.5,重度脂肪肝L/S≤0.5。常规CT能定量诊断中、重度的脂肪变性,特异度为100%,灵敏度为82%,但对轻度脂肪肝的诊断价值较低^[11]。有研究^[12]表明,只有肝脂质浸润超过30%,常规CT才有较高的诊断准确度。贺文等^[13]以肝穿刺活检为金标准,证实肝血管相对密度定量诊断脂肪肝的准确度为93.1%,而用CT阈值定量诊断脂肪肝的准确度仅为65.9%,并且与CT阈值诊断脂肪肝相比较,CT扫描机系统误差对诊断结果的影响较小。

1.2 双能CT (dual-energy CT, DECT)

利用高低两种不同能量的X射线扫描物体得到被扫描物体的电子密度和有效原子序数。

Artz等^[14]的一项动物研究显示,DECT与小鼠血清甘油三酯及肝脏质子密度脂肪分数磁共振成像(magnetic resonance imaging of liver proton density fat fraction, MRI-PDFF)测值的相关性良好, r^2 分别为0.89、0.86;此研究还表明,与单能量CT相比较,DECT的线性回归也得到了极好的相关性($r^2=0.88$)。Hyodo等^[15]采用DECT多物质分离(multi-material decomposition, MMD)算法计算脂肪体积分数(fat volume fraction, FVF),得出DECT区分病理学分级S0与S1~3的FVF实际截断值为5%,阳性预测值为100%,该研究表明基于双能量CT的MMD算法用于肝脏脂肪定量的准确性和重复性较好。

1.3 低剂量CT衰减校正扫描 (low-dose CT attenuation correction, CTAC)

Ahmed等^[16]的研究表明,CTAC诊断MAFLD的灵敏度为81.3%、特异度为94.0%、阳性预测值为60.2%、阴性预测值为97.8%,其阳性预测值相对比较低,所以CTAC可用于排除MAFLD。

CT对操作者的依赖性低,一般平扫即可,DECT和低剂量CT衰减校正扫描对脂肪肝的定量诊断潜能大,但目前主要在研究阶段,尚未在临床广泛应用。此外,有研究^[17]表明,除脂质沉积会导致肝CT值的变化以外,其他物质在肝内的沉积及弥漫性肝病也会引起肝脏CT值改变,如甲氨蝶呤、肝硬化等。

2 磁共振检查

磁共振检查MAFLD的技术包括磁共振成像(magnetic resonance imaging, MRI)、磁共振波谱成像(magnetic resonance spectroscopy, MRS)、MRI-PDFF。其检测肝脂肪变性的信号来源主要是水分子(自由水)和脂肪组织(甘油三酯)中的H质子。

2.1 MRI

利用化学位移成像(chemical shift imaging, CSI)显示肝脏脂肪沉积的图谱,该技术采用Dixon方法,即基于两点化学位移的油脂-水分离方法^[18]。MRI对轻度脂肪变性的检测灵敏度为63.7%~92.2%,特异度为81.0%~94.9%^[19-20]。该

技术受空间分辨力、层厚、矩阵以及铁沉积、纤维化等影响,对肝内脂肪变性的评价只是定性的,无法进行准确的量化评价^[21]。

2.2 MRS

和CSI的原理相同,利用化学位移的作用获取水和甘油三酯同反相位的波谱,MRS几乎可以探测甘油三酯的所有成分的波峰,通过分析波峰的变化反应代谢的情况^[22]。MRS多采用单体素技术并选择激励回波采集序列,对肝脂肪变性进行半定量诊断,其诊断灵敏度为80%,远高于CT与常规超声^[23]。2017亚太地区MAFLD病指南^[1]及EASL指南^[24]提出MRS是临床试验中监测轻微脂肪变性的最佳选择,但技术复杂、取样局限、受呼吸影响,其成功率仅为60%~80%。

2.3 MRI-PDFP

MRI-PDFP采用m-DIXON序列和IDEAL-IQ序列,通过计算脂肪在肝实质中所占的体积比进行脂肪含量的量化分析,准确反映脂肪肝程度,并且能预测MAFLD患者的肝纤维化进展^[25]。Tang等^[26]的研究表明,MRI-PDFP诊断肝脂肪变性 $\geq S1$ 的灵敏度为86%,特异度为83%;诊断肝脂肪变性 $\geq S2$ 的灵敏度为64%,特异度为96%;诊断肝脂肪变性 $\geq S3$ 的灵敏度为71%,特异度为92%。Dong等^[27]的研究证实,MRI-PDFP与肝脏穿刺病理脂肪定量结果呈很好的正相关性,是目前理想的脂肪定量方法,具有高分辨率连续脂肪分布图像,成功率接近100%,操作简单,耗时短,但费用较昂贵。

3 超声检查

3.1 常规超声检查

根据肝实质回声强弱、后场衰减程度、肝肾回声对比增强、门静脉管壁回声、膈肌清晰显示度等将脂肪肝初步评估为轻、中、重度^[28-30]。常规超声诊断轻度肝脂肪变性($>5\%$)的灵敏度仅为60.9%~65%^[8, 30],诊断中-重度肝脂肪变性的灵敏度为84.8%,特异度为93.6%,受试者工作特征曲线的曲线下面积(area under curve, AUC)为0.93(0.91~0.95)^[29]。但常规超声诊断MAFLD主观性强,观察者内及观察者间的差异大。

3.2 肝肾比(hepatorenal ratio, HRR)半定量评分

采用直方图或分析软件计算肝肾回声强度比值进行半定量分析;Borges等^[31]以健康人为对照,指出HRR诊断MAFLD的灵敏度为92.7%,特异度为92.5%。Marshall等^[32]以肝组织活检为金标准进行对照,指出当HRR ≥ 1.28 时诊断轻度肝脂肪变性($>5\%$),灵敏度为100%,特异度为54%。HRR半定量评分诊断MAFLD,操作简单,但主观性强,准确度低,检测轻度脂肪变性灵敏度低。

3.3 超声定量方法

利用脂滴小界面对超声波的散射,通过分析超声原始射频信号,计算背向散射系数(backscatter coefficient, BSC)或衰减系数或声速进行定量;包括BSC、受控衰减参数(controlled attenuation parameter, CAP)、声衰减成像(attenuation imaging, ATI)、声衰减系数(attenuation coefficient, AC)、超声引导衰减参数(ultrasound-guided attenuation parameter, UGAP)、声速估计(speed of sound estimation, SSE)。超声定量方法客观性及准确性较好,受仪器调节等因素影响小,但对软件或算法要求高。

3.3.1 BSC

BSC是对探头接收的超声波散射信号用计算机进行后处理进而评估肝脂肪变。Lin等^[33]研究表明,实验组中BSC诊断MAFLD的灵敏度为93%,特异度为97%,阳性预测值为99%,阴性预测值为86%;在对照组中BSC诊断MAFLD的灵敏度为87%,特异度为91%,阳性预测值为95%,阴性预测值为76%。该方法可在任何超声系统上运行,可重复性好,不依赖于操作者和系统^[34],是组织的基本物理属性,准确性高;但技术复杂,需要使用体模,目前仍处于实验研究阶段,尚未在临床应用。

3.3.2 CAP

运用瞬时弹性扫描仪(法国Echosens公司的FibroScan)检测肝脏硬度值的同时对肝脏衰减参数进行测量来定量诊断肝脏脂肪含量的工

具,是目前研究最多的超声定量方法^[35]。Wang等^[36]的研究显示,CAP诊断肝脂肪变性($\geq 10\%$)的截断值为275 dB/m,灵敏度为87.5%,特异度为72.2%,阳性预测值为84.4%;CAP诊断肝脂肪变性($\geq 20\%$)的截断值为325 dB/m,灵敏度为70.0%,特异度为85.0%,阴性预测值为91.9%。2012年,Sasso等^[37]对合并慢性丙型肝炎的MAFLD患者进行CAP检测,发现CAP测值与肝脂肪程度相关,不受肝纤维化的影响,这与中国学者徐晓鸾等^[38]对合并慢性乙型肝炎的MAFLD患者的研究相一致。CAP检测MAFLD可重复性较好,准确性较高,操作失败率低,亚太指南^[1]建议将CAP作为MAFLD筛查工具。但不同研究报道的诊断阈值及效能差异较大,不同程度的诊断阈值重叠,不同型号探头的诊断阈值不确定;而且CAP缺乏二维图像引导不能对肝脏进行形态学评估,测值影响因素较多;对治疗效果的随访研究目前报道较少。

3.3.3 ATI

ATI是日本Canon公司推出的一项检测脂肪肝的新技术,利用发生脂肪变性的肝组织对声波的衰减进行检测,该技术不仅定量而且实时成像,采用大取样框成像,计算时能自动屏蔽非目标结构(血管等)和强伪像(混响伪像)的干扰,不需要采集数据进行后期处理计算,可直接得出定量数值,不受超声系统设置或调解的影响,质量控制R²模式有利于准确有效测量^[39]。Ferraioli等^[40]研究显示,以MRI-PDFF为参考,与MRI-PDFF的相关性ATI($r=0.81$)明显高于CAP($r=0.65$);而且S0~1 vs S2~3的ATI AUC为0.95,CAP AUC为0.88;S0 vs S1~3的ATI AUC为0.91,CAP AUC为0.85;ATI的测值可重复性高,观察者内相关系数为0.81~0.98,观察者间相关系数为0.792~0.92。Tada等^[41]的研究表明,ATI对轻度脂肪肝诊断效能较高,诊断S1($\geq 5\%$)的灵敏度为67.8,特异度为87.6%,阴性预测值为80.4%。ATI作为一项新技术对不同病理学分级的肝脂肪变诊断价值较高。

3.3.4 AC

AC利用探头发射不同频率(f_0 、 f_1 ,

$f_0 < f_1$)超声波,通过计算获得的接受信号比率的斜率来确定ATT(f_0/f_1)。该方法测量时感兴趣区(region of interest, ROI)需避开大的管道结构,可实时获得该段的AC,但只能定量测量,不能成像^[34]。闫珊玲等^[42]的研究显示,AC与MRS测定的肝脏脂肪含量相关性显著,对轻度脂肪肝的诊断灵敏度、特异度分别为81.4%、100.0%明显优于常规超声(灵敏度47.6%、特异度70.3%)。Paige等^[43]的研究表明,在对照组中AC对脂肪肝分级诊断的准确度为61.7%,高于常规超声检查的51.7%,而且操作者间有较好的一致性。

3.3.5 UGAP

Fujiwara等^[44]研究表明,UGAP诊断肝脂肪变性 $\geq S1$ 的灵敏度为81.2%,特异度为87.1%;诊断肝脂肪变性 $\geq S2$ 的灵敏度为85.7%,特异度为81.5%;诊断肝脂肪变性 $\geq S3$ 的灵敏度为80.4%,特异度90.0%,以上结果均高于CAP测值结果;该研究同时还指出UGAP诊断肝脂肪变的观察者内相关系数为0.86,观察者间相关系数为0.84,高于Ferraioli等^[45]证实的CAP观察者间的一致性(0.82)。UGAP的不足之处在于需要参考体模进行后期计算,过程较繁琐,而且没有衰减成像。

3.3.6 SSE

该技术基于肝脏中脂肪的增加导致声速下降,在优化背向散射斑点噪音的基础上初步估测声速,同时创建虚拟点状发射器,发现并纠正正在第一传播层中产生的偏差及由被测者皮下层厚度导致的偏倚^[46],Dioguardi等^[47]研究表明,当SSE的截断值 ≤ 1.537 mm/ μ s,诊断肝脂肪变S1~S3的灵敏度为80%,特异度为85.7%,与MRI-PDFF的相关性良好。

综上所述,CT因其辐射暴露、可重复性差、对轻度脂肪肝诊断价值低等原因不作为临床筛查MAFLD的首选。MRI、MRS、MRI-PDFF诊断MAFLD的准确度高,但其价格昂贵,受地域经济限制,无法普及,不适用于筛选。超声技术操作简单便捷,其中部分定量技术可在超声系统

上运行, 准确度较高, 有助于客观、量化评估肝脏脂肪变程度, 但目前大部分尚在研究阶段。

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