·综　述·

非酒精性脂肪性肝病的超声无创评估技术进展

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［摘要］ 非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）是世界范围内最见的弥漫性肝病之一。约1/3的NAFLD会发展为非酒精性脂肪性肝炎，导致不同程度的肝纤维化或肝硬化，增加肝癌的患病风险。对NAFLD早期识别和分级评估，并进行积极干预，对延缓病程发展至关重要。肝穿刺活检是量化肝脂肪变性的金标准，但其为有创操作，且存在取样误差。超声检查具有简便、实时、无创等优势，被指南推荐为NAFLD首选的影像学诊断手段。本文综述近年来超声新技术在NAFLD诊断中的应用进展。

［关键词］ 非酒精性脂肪性肝病；脂肪变性；超声；背向散射；声衰减系数；声速

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Technical progress in noninvasive ultrasound evaluation of non-alcoholic fatty liver disease

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［**Abstract**］ Non-alcoholic fatty liver disease (NAFLD) is one of the most common diffuse liver diseases worldwide. Approximately one-third of NAFLD will develop into non-alcoholic steatohepatitis, liver fibrosis, and even cirrhosis, and increasing the risk of liver cancer. Early diagnosis, grading and active intervention of NAFLD are essential to postpone the disease progression. The pathology of liver biopsy is the gold standard for quantifying steatosis of liver. However, it is an invasive operation with potential sampling errors. Ultrasound examination is recommended as the first line imaging diagnostic program for NAFLD by the guidelines, with the advantages of convenient, real time and non-invasive. This article reviewed the recent advances in the application of novel techniques based on ultrasound in the diagnosis of NAFLD.

［**Key words**］ Non-alcoholic fatty liver disease; Steatosis; Ultrasound; Backscatter; Attenuation coefficient; Sound speed

随着全球经济发展和人们生活方式的改变，非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）已成为常见的肝脏疾病之一，发病率达25.24%[1-2]。NAFLD根据病程分为两个阶段：非酒精性脂肪肝（non-alcoholic fatty liver，NAFL），约1/3的NAFLD发展为非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH），进而导致不同程度的肝纤维化或肝硬化，增加肝癌的患病风险[3-4]。早期诊断NAFLD并进行及时干预，对延缓病程发展至关重要。肝脏穿刺活检是用于NAFLD诊断和分级的金标准，但其为有创操作，且穿刺活检的取样标本局限，无法全面评估肝脂肪变性状态。因此，在临床工作中亟待一种简单、无创、定量、可动态随访和评估疗效的影像学检测方法。超声检查凭借其无创、实时、灵活等独特优势，被欧洲肝脏协会发布的《非酒精性脂肪肝管理临床实践指南》推荐为NAFLD首选的影像学诊断手段[3]。本文就近年来层出不穷的NAFLD超声无创评估新技术及其应用研究进展进行综述。

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1 B型超声（B–mode ultrasound，BMUS）

BMUS是定性评估脂肪肝的常用工具，根据声像图表现可分为正常、轻度（肝实质回声稍增强）、中度（可伴有右肝后叶实质回声衰减或膈肌显示不清，门脉管壁回声减低）和重度（肝实质回声衰减范围达到前叶，肝内血管壁模糊）[5]。BMUS的不足之处在于受仪器调节和操作者主观性的影响，不能精准地判断脂肪肝程度[6-7]。

2 超声半定量方法

肝肾指数（hepatorenal index，HRI）检测技术主要通过比较感兴趣区（region of interest，ROI）内肝实质与肾皮质回声强度来诊断脂肪肝。研究[8]显示，HRI诊断肝脂肪变性程度的受试者工作特征曲线的曲线下面积（area under curve，AUC）为0.73~0.89，与目前作为NAFLD诊断参考标准的磁共振成像质子密度脂肪分数（magnetic resonance imaging-proton density fat fraction，MRI-PDFF）具有一致性，与病理学检查结果相关性高。HRI技术在一定程度上可避免操作者主观视觉的影响[9]，但不同研究[9-10]之间诊断阈值有差异（1.28~1.49），且不能全面地反映肝脏组织的情况。当患者合并急慢性肾病，或是右肾缺如、手术切除的情况，则影响HRI检测[10]。

3 超声定量评估肝脂肪含量

为解决定性和半定量技术的不足，客观性好、准确度高的定量超声技术应运而生。基于光谱技术利用脂滴小界面对超声波的散射，可计算衰减系数（即检测组织内单位距离上能量损失）和背向散射系数（即检测组织中的超声回波信号）[11-12]，基于统计学分析技术通过运用声学结构定量、局部方差归一化和声速计算来实现对肝脂肪含量的定量评估。

3.1 受控衰减参数（controlled attenuation parameter，CAP）

CAP采用瞬时弹性扫描仪FibroScan，通过测量肝脏硬度值和肝脏衰减参数，对于肝脏脂肪含量大于10%的肝脂肪变性进行定量评估[13]。亚太指南[14]推荐将CAP作为NAFLD的筛查工具。CAP技术的优势在于可以无创、便捷地诊断肝脂肪变性，不受纤维化的影响[13]。但研究[13, 15-16]表明，CAP的AUC（0.73~0.95）低于MRI-PDFF（0.90~0.99）。CAP诊断阈值存在重叠。一项meta分析[17]发现，CAP诊断轻度、中度和重度脂肪变性的阈值分别为248、268和280 dB/m。然而Moret等[18]的研究结果显示，CAP诊断轻度、中度和重度脂肪变性的阈值分别为271、331和355 dB/m。CAP技术的不足之处还在于检查过程中需要更换专用探头，缺乏BMUS图像实时引导[7]，测量的失败率达7.7%~14%[19-22]。

3.2 声衰减成像（attenuation imaging，ATI）

ATI技术基于衰减系数的检测［单位dB/（cm·MHz^{-1}）］[7]，BMUS和ATI双幅实时显示。据报道，ATI技术与MRI-PDFF的一致性较CAP更高[23]，ATI的观察者内和观察者间一致性分别为0.929和0.792[24]，多次测量的可重复性好［组内相关系数（intra-class correlation coefficient，ICC）为0.85~0.86］[25]。在一项分析患者性别、年龄、体重指数（body mass index，BMI）、实验室指标（血清高密度脂蛋白、低密度脂蛋白、葡萄糖等）和肝脂肪变性病理学分级对ATI测值的影响因素研究[26]中，结果显示病理学分级是ATI测值的独立影响因素（$P<0.001$），另两项研究[27-28]也支持此结论。在应用ATI技术进行诊断或随访时，应尽量选择相同模式，以避免不同模式频率对测值的影响[23]。

3.3 声衰减技术

声衰减技术原理是基于探头在同一声束方向连续发送和接收两种频率的超声波，根据接收到的信号振幅差值和斜率，得到衰减系数。可检测的深度范围为4~10 cm，不受患者皮下脂肪厚度的影响。据报道，声衰减技术的测值与肝脂肪变性程度呈正相关[29]，诊断效能高（AUC=0.868）[30]。此前的一项多中心前瞻性研究[31]对纳入的351例慢性肝病患者分别行肝脏穿刺活检和声衰减技术检查，结果也显示声衰减技术诊断效能高，诊断轻度、中度、重度肝脂肪变性的AUC分别为0.79、0.87和0.96，阈

值分别为0.63、0.69和0.85 dB/（cm·MHz^{-1}）。声衰减技术的优势在于操作时可在BMUS引导下放置ROI，有助于提高声衰减技术检测的成功率[32]，但无法调节ROI。目前未见声衰减技术的测值与MRI-PDFF测值相关性的研究报道，也缺乏声衰减技术对评估NAFLD病情的研究。

3.4　超声引导声衰减参数（US-guided attenuation parameter，UGAP）

UGAP技术原理是基于已知衰减系数的参考体模，利用补偿的方式获取肝脏超声回波信号，在最佳测量范围内测量斜率，计算得出衰减系数[33]。研究显示，UGAP测值与CAP、ATI和MRI-PDFF测值存在相关性（r=0.730~0.803）[33-35]，且不受肝脏硬度值增加的影响[36-37]。UGAP诊断准确度高，诊断S1、S2和S3级脂肪变性的AUC分别为0.89~0.90、0.91~0.95和0.91~0.95[34，38]。UGAP的技术优势还在于可提供质量图、衰减图，可重复性好[39]，操作成功率为98.3%~100%[34，40]。但是，有研究指出UGAP技术对脂肪变性程度方面的诊断阈值存在重叠[33，41]，对轻度脂肪变性的诊断准确度欠佳[36]。因此，UGAP技术的临床价值还需更多研究样本进行验证。

3.5　背向散射系数（backscatter coefficient，BSC）

当脂肪细胞体积增大，与正常肝组织之间的声阻抗差增大，背向散射便会增强[12]，基于这一原理，BSC技术可获取类似于BMUS回声特征的射频回波定量数据[42-43]。据报道，不同超声仪器之间BSC测值的一致性较好，不受患者BMI和检测深度的影响[44]，可重复性好（ICC=0.69~0.95）[43，45]。BSC测值与MRI-PDFF的测值具有相关性（ρ=0.8），诊断NAFLD的AUC为0.98，阈值为0.003 8/cm-sr[12]。但BSC技术的不足之处在于，并非所有超声仪器都能记录和输出超声射频回波信息，获取的数据还需外部体模校准，临床应用范围受限[45]。

3.6　超声脂肪分数（US-derived fat fraction，UDFF）

UDFF技术通过测量组织回波射频信号中的衰减系数和BSC，计算得出反映肝脏脂肪含量的UDFF（%），推荐以5%为鉴别肝脏脂肪含量正常与否的标准。在BMUS实时引导下，启动UDFF模式，确定一个大小为3 cm×3 cm的ROI，同时激活自动点式剪切波弹性成像功能，获得剪切波速度（m/s）和杨氏模量值（kPa）。在检测过程中，ROI可自动屏蔽运动伪像、肝内大的管道或肝包膜等区域，避免测量误差。一项前瞻性研究[46]证实UDFF可重复性高（ICC=0.93~0.98），不受BMI和测量深度的影响，但该研究样本量偏少（21例成人），缺少病理学对照。Labyed等[47]的前瞻性研究对101例NAFLD患者（其中90例接受了肝脏穿刺活检）进行UDFF与MRI-PDFF的一致性和诊断效能分析，结果显示UDFF与MRI-PDFF测值存在线性相关（ρ=0.87），UDFF诊断轻度、中度和重度脂肪变性的AUC分别为0.94（灵敏度84.0%，特异度100.0%）、0.88（灵敏度77.0%，特异度89.0%）和0.83（灵敏度100.0%，特异度65.0%），对应的诊断阈值分别为8.1%、15.9%和16.1%。另一项前瞻性研究[48]也得到相似的结果，UDFF与MRI-PDFF测值正相关（ρ=0.82），UDFF的AUC为0.9，灵敏度为94.1%，特异度为63.3%。

UDFF技术的优势在于，UDFF与MRI-PDFF测值呈线性相关，而衰减系数、BSC技术测值与MRI-PDFF测值呈非线性相关[47-48]。因此，UDFF可与MRI-PDFF直接对照，且与MRI-PDFF相比，UDFF更加经济、便捷。UDFF采用DAX探头，测量深度可达55 cm，适用于体型较大或BMI较高的患者。鉴于目前有关UDFF这项新技术的研究甚少，其临床应用价值还需多中心、大样本的研究进行验证。

3.7　声学结构定量（acoustic structure quantification，ASQ）

ASQ技术原理是基于统计学χ^2检验，通过比较正常肝脏和实测肝组织超声波振幅分布，读取并量化脂肪变性之后肝实质回声的变化信息，计算得出C_m^2和焦点干扰（focal disturbance，FD）比率[49-50]。研究证实，C_m^2值的大小可

反映实测肝组织与正常肝脏声学特性的差别，C_m^2值增大则提示肝硬化程度越高[51]，而FD比率与肝脂肪变性程度之间存在密切关系[52]。Karlas等[53]分析了ASQ参数（mode值、均值和FD比率）与肝纤维化程度（由瞬时弹性成像和NAFLD纤维化评分评估）和肝脂肪变性（由CAP测值评估）的相关性，该研究纳入50例有NAFLD患病风险的2型糖尿病患者和20位健康志愿者（对照组），均行MRI-PDFF、瞬时弹性成像、CAP和ASQ检查。结果显示，ASQ参数在对照组和糖尿病患者之间差异有统计学意义（$P<0.001$），ASQ参数与脂肪变性存在相关性（$P<0.05$），而所有ASQ参数与纤维化程度无相关性（$P>0.08$）[53]。但Toyoda等[54]的研究分析了148例经病理学检查证实为慢性丙型肝炎患者的ASQ参数C_m^2直方图峰值与肝脏纤维化之间的相关性，结果显示峰值随着纤维化等级增高而升高。

因此，ASQ技术的优势在于可从脂肪变性和纤维化程度两个方面评估NAFLD[51，55-56]。但是，ASQ技术的不足之处在于需要搭配外部分析软件，缺少BMUS图像对照，需要获取7个参数和1幅红蓝曲线图[51]，分析方法繁杂。在操作时，与上腹部和肋下扫查相比，肋间隙扫查获得的ASQ参数更能真实地反映肝脏脂肪成分的变化[57]。

3.8 局部方差归一化（normalized local variance，NLV）

NLV是ASQ技术的改进，基于对肝脏BMUS图像振幅信息分析的原理评估组织均匀性[58]。在BMUS引导下放置合适大小的ROI，一次获得5个NLV值。NLV技术的可重复性较好（ICC=0.930）[59]，与肝脂肪变性的程度具有相关性，诊断效能较高，诊断≥S1级的AUC为0.911（阈值1.095），≥S2级的AUC为0.974（阈值1.055），≥S3级的AUC为0.954（阈值1.025），肝脂肪变性是NLV的独立影响因素（$P<0.001$）[58]。但是目前的研究人群肝脂肪变性分布不均，NLV的诊断效能和对肝脏纤维化的诊断还需大样本研究验证。

3.9 组织衰减成像（tissue attenuation imaging，TAI）和组织散射分布成像（tissue scatter-distribution imaging，TSI）

TAI和TSI技术源于韩国Samsung公司的RS系列超声仪器，前者基于声衰减，后者通过量化实测肝脏的背向散射信号与正常肝脏的瑞利分布之间的相关性来显示散射分布情况。研究显示，TAI、TSI可重复性高（ICC为0.947~0.994），与CAP、MRI-PDFF和脂肪变性病理学等级存在相关性，AUC为0.827~0.917，TAI和TSI诊断阈值分别为−0.078 MHz/cm和0.910，测值不受肝脏纤维化影响[60-62]。但考虑到现有研究可能存在的研究对象选择偏倚[62]，TAI和TSI技术的临床应用价值还需多中心、大样本的研究证实。

3.10 基于声速的超声定量技术

声速定量检测技术基于超声波在不同脂肪含量组织内传播速度不同，肝脏脂肪含量增加可导致超声波声速降低的原理。研究显示，声速定量检测技术可重复性好（ICC=0.93）[63]，与MRI-PDFF存在较高的相关性，诊断效能AUC为0.880~0.952，阈值为1 524~1 555 m/s，CAP测值和患者腹围是声速测定的独立影响因素[64-65]。该技术的不足之处在于测量值受皮下和肝脏周围组织的影响[63，65]。

4 人工智能方法

基于人工智能的超声组学技术，通过数据收集和整理、病灶分割、高通量特征提取和量化、特征选择，再通过机器学习构建模型，在一定程度上可有效、精准、客观地分析疾病特征、评估疗效和预后[66]。陈明丽等[67]对BMUS图进行纹理分析，从中提取14个参数用于诊断早期肝硬化，诊断效能AUC达0.93。该团队的研究还进一步利用主成分分析法，在不降低诊断效能的情况下，减少了数据量[68]。超声组学技术的发展成熟有赖于大量、标准化的医学图像，但是超声图像的标准化采集存在挑战性，影响后期图像ROI勾画、特征提取和模型效能的稳定性。

5 总结与展望

NAFLD是全世界范围内最常见的肝脏疾病，早期识别NAFLD并进行积极干预至关重

要。超声无创的评价手段，尤其是定量检测技术的发展，能够准确地评价肝脂肪变性，具有便捷、高效的优势。但目前各类超声新技术临床应用证据较少，其诊断效能、诊断阈值及与MRI-PDFF的相关性或一致性等，仍需要未来多中心的高质量临床研究验证。

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