Chiyanika C, et al., Arch Clin Biomed Res 2023
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Table 4: Pairwise comparisons of area under receiver operating characteristic curves of the imaging methods for detecting various hepatic steatosis grades.

ATI vs. PDFF	**S0 vs. S1-S3 (S>0)**	**S0-S1 vs. S2-S3 (S>1)**
Difference between areas	0.0982	0.04
Standard Error [a]	0.0932	0.0422
95% Confidence Interval	-0.0845 to 0.281	-0.0428 to 0.123
z statistic	1.054	0.947
Significance level	p=0.292	p = 0.344
ATI vs. MRS		
Difference between areas	0.0982	0.08
Standard Error [a]	0.0932	0.0951
95% Confidence Interval	-0.0845 to 0.281	-0.106 to 0.266
z statistic	1.054	0.841
Significance level	p=0.292	p = 0.400
PDFF vs. MRS		
Difference between areas	0	0.12
Standard Error [a]	0	0.0938
95% Confidence Interval	-	-0.0639 to 0.304
z statistic	-	1.279
Significance level	p=1.000	p = 0.201

[a]DeLong test. ATI= attenuation imaging, MRS= magnetic resonance spectroscopy, PDFF= proton density fat fraction, S=steatosis grade.

grade 1 (S0-1 vs. S2-3), and 0.93 (0.69-1.00, p<0.001, for grade 2 (S0-2 vs. S3). The corresponding Youden's index, sensitivity, specificity as well as the AUROCs of MRI-PDFF and proton-MRS are shown in Table 3.

There were no significant differences on pairwise comparison of the AUROCs of the imaging methods (ATI, MRI-PDFF and proton-MRS) for detecting S> grade 0 and S> grade 1, as summarised in Table 4. Due to limited sample size, data were insufficient for a pairwise comparison of the AUROCs for detecting S> grade 2.

Discussion

In this study, ATI showed a significant correlation with MRI-PDFF, and proton-MRS. ATI also showed a significant correlation with liver steatosis grade as determined by histology, but not with NAS activity score and fibrosis stage. The diagnostic performance of ATI for detecting liver steatosis greater than grades 0,1 and 2 were 0.91, 0.97 and 0.93, respectively. The diagnostic performance of ATI, MRI-PDFF and proton-MRS were shown not to be significantly different in detecting various liver steatosis grades. The strength of this study lies in the use of subjects who had liver biopsy and within a short interval between biopsy and imaging. The success of ATI in this morbid obese cohort with liver steatosis without any other underlying liver pathologies is another strength. The comparison of ATI with both MRI-PDFF and proton-MRS which has not been assessed in previous studies further adds to the strength of the study.

ATI showed a strong correlation with steatosis grade (r=0.833). Bae et al [25]. in a study involving 108 patients with histology proven steatosis showed the correlation coefficient of ATI with steatosis grade of 0.660. Likewise, Tamaki et al [26] in a study involving 351 patients showed a correlation coefficient of 0.470. Similarly, Huang et al [27] showed a correlation of 0.721 between ATI and steatosis grade. Variations in the correlation coefficients in these studies could be attributed to the varying BMIs, sample sizes, mixed liver aetiologies, and ethnicities used. Moreover, Nazare et al [28] showed that ethnicity significantly affects liver fat distribution, while Fan et al [29] showed that BMI (even in dose dependent manner) was associated with fatty liver risk. Indeed, our study cohort had no known other liver pathologies as was in other studies. It was further shown that ATI did not correlate with NAS activity score and fibrosis stage, in agreement with previous studies [25,26]. These outcomes may imply that ATI may not be affected by inflammation/fibrosis and therefore a poor marker for both conditions, yet it reassures that ATI seems to only determine the fat content in the liver without being affected by the presence of inflammation/fibrosis. However, more studies linking ATI with necroinflammatory activity score, or fibrosis stage are needed to confirm this outcome.

In this study, the diagnostic accuracy (AUROC) of ATI in detecting liver steatosis grades 1, 2 and 3 were 0.91, 0.97 and 0.93 respectively. The associated AC cut-off points for the above steatosis grades were: 0.59cm/dB/MHz, 0.60cm/dB/MHz, and 0.63cm/dB/MHz, respectively. These outcomes are similar to previous studies [16, 25, 26, 30-37]. It was also shown that pairwise comparison of AUROCs of the imaging methods did not show any significant differences. These results suggest that ATI may be a useful non-invasive tool to quantify liver steatosis. They further imply that ATI may be a reliable method to quantify hepatic fat even in subjects with morbid obesity, and its usefulness may enable early detection of liver steatosis at a relatively low cost. This could allow "mass screening" to be possible for purposes of either general population studies on NAFLD or for early detection of liver steatosis. This might particularly be helpful in encouraging lifestyle changes before marked hepatic damage occurs. However, the AC range of steatosis grade 0 was shown to overlap with the AC range of steatosis grade 1, unlike the outcome of both MRI-PDFF and proton-MRS. Like our findings, we also noticed this overlap in previous studies [16,25,26,30-37]. These outcomes suggest that ATI may not be as sensitive as MRI-PDFF/proton-MRS for distinguishing between steatosis grades 0 and 1, and care must be taken when using ATI as some cases may be allocated as being

Chiyanika C, et al., Arch Clin Biomed Res 2023
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positive or negative when in fact not. Under such suspicious circumstances, MRI-PDFF can be used to confirm the outcome. Notwithstanding the above argument, ATI seems to be reasonably more sensitive in detecting severe forms of steatosis (grades 2 and 3).

Our study, together with previous studies showed a variation in AC cut-off points for various steatosis grades (i.e., 0.56- 0.63cm/dB/MHz for steatosis > 0; 0.59-0.72cm/dB/MHz for steatosis > 1; and 0.69-0.94cm/dB/MHz for steatosis > 2) [16, 26, 30, 32, 34, 38-40]. This variation in AC cut-off points in these studies could in part be explained by use of transducers of varying frequencies (mostly 3 and 4MHz as reference frequencies), especially that attenuation is directly related to transducer frequency (the higher the frequency, the higher the attenuation). However, this variation further suggests that presently, ATI has no standardised cut-off points as is the case with MRI, hence the need for more validation studies involving large sample sizes, in multiple centres, and using a homogenous transducer reference frequency.

The major limitation of this study is the small sample size, which could account for our findings, and this was because of COVID-19 pandemic as all elective surgical cases were suspended. However, the results obtained in this study are comparable to few available studies on ATI which had larger sample sizes, thus, care must be exercised when interpreting these results. ATI examinations were conducted by a single operator, thus, interobserver agreement could not be assessed. Nonetheless, inter-observer correlation of ATI has been shown to range from 0.91-0.98 [13, 33, 41-44]. Finally, the cohort was of Chinese ethnicity, therefore, caution should be taken in the generalisation of the results.

Conclusion

ATI is a promising non-invasive tool in quantifying hepatic fat, whose diagnostic performance is not significantly different to MRI-PDFF and proton-MRS. Future multicentre studies with large sample sizes in subjects with histologically proven liver steatosis and a control group may be needed to further validate this modality, especially that currently there is non-availability of standardized attenuation coefficient cut-off values for each corresponding steatosis grade in various ethnic groups and BMIs.

Author Contributions

The roles of CC in the study were: conceptualization, data curation, formal analysis, investigation, methodology. WC roles were in: methodology, project administration, resources, supervision, writing, review & editing. KHL roles were in: investigation, supervision, writing, review & editing. VW roles were in: validation, writing, review & editing, supervision. CC and WC were involved in investigation and analysis. WC sourced the project funding. All authors agreed to be accountable for all aspects of the work.

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