Quantitative Detection of Cirrhosis: Towards the Development of Computer-Assisted Detection Method

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Abstract There are distinct morphologic features of cirrhosis on CT examinations; however, such impressions may be subtle or subjective. The purpose of this study is to build a computer-aided diagnosis (CAD) method to help radiologists with this diagnosis. One hundred sixty-seven abdominal CT examinations were randomly divided into training ($n=88$) and validation ($n=79$) sets. Livers were analyzed for morphological markers of cirrhosis and logistic regression models were created. Using the area under curve (AUC) for model performance, the best model had 0.89 for the training set and 0.85 for the validation set. For radiology reports, sensitivity of reporting cirrhosis was 0.45 and specificity 0.99. Using the predictive model adjunctively, radiologists' sensitivity increased to 0.63 and specificity slightly decreased to 0.97. This study demonstrates that quantifying morphological features in livers may be utilized for diagnosing cirrhosis and for developing a CAD method for it.

Keywords Computed tomography · Quantification · Computer-assisted image interpretation · Computer aided diagnosis · Cirrhosis

Abbreviations

AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
AUROC	Area under receiving operating characteristic
BSA	Body surface area
CAD	Computer-aided diagnosis
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
MELD	Model of End-Stage Liver Disease
MR	Magnetic resonance
STL	Stereolithography

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Introduction

There are distinct morphologic features which can identify the presence of cirrhosis on CT imaging, however, impressions can often be subjective and not standardized. In particular, it may be difficult for radiologists to distinguish cirrhosis in patients who have significant fibrosis but have not yet developed cirrhosis or patients with early cirrhosis. The purpose of this study was to develop a computer aided diagnosis (CAD) tool which can help identify cirrhosis by quantifying morphologic features in cirrhosis, and which functions along the entire spectrum of liver disease.

The purpose of this study was not to develop another automated liver segmentation algorithm. Liver segmentation is a separate field of study in and of itself [1]. This work

focused on developing a CAD tool based on quantifying morphologic features using a segmented liver, regardless of how the liver was segmented.

The development of cirrhosis in a patient with chronic liver disease represents an important clinical landmark. The clinical guidelines for the care of patients with cirrhosis are very different than those for patients without cirrhosis, such as medication choices, need for hepatocellular cancer screening, and vaccination [2, 3]. At the present time, a liver biopsy is still considered the gold standard for the diagnosis of cirrhosis [4], however it has several drawbacks. First, there is a small but not insignificant risk of morbidity and mortality [5], including pain in up to 84 % of patients and bleeding in 0.1 to 2 %. Even death has been reported to occur in approximately 0.1 % of cases after liver biopsy. Furthermore, there are issues of sampling error as only about 1/50,000 of the liver volume is sampled, as the geographic distribution of cirrhosis is not uniform. In addition, there is a 10–20 % inter-observer discrepancy among pathologists.

There has been a tremendous amount of interest in developing non-invasive methods to assess for liver fibrosis and cirrhosis [4, 6–8]. These essentially fall into three different categories: (1) analysis of indirect serum biomarkers of fibrosis, (2) direct serum biomarkers of fibrosis and (3) different imaging modalities. Many of the indirect markers of serum fibrosis are the most cost effective and easy since they are based on common biochemical studies such as serum AST, ALT, and platelet counts. However, the overall sensitivity and specificity are generally not sufficient. Direct markers of fibrosis suffer from sensitivity and specificity issues in part due to the fact that they represent matrix turnover markers and thus are increased in the presence of any inflammation.

The most promising modality to diagnose fibrosis and cirrhosis is imaging. Transient ultrasound elastography and acoustic radiation force impulse have been useful but they require specialized equipment that is not readily available in the USA [9]. In addition, these techniques cannot be used for obese patients, which represent a very significant proportion of the population requiring evaluation for liver disease.

Magnetic resonance (MR) elastography and MR spectroscopy are additional imaging modalities requiring highly expensive and specialized equipment [10].

Given the ubiquity of CT imaging, we sought to develop a quantitative method of diagnosing cirrhosis using standard incidental CT scans.

Only few prior reports exist on using CAD with CT scans to diagnose chronic liver disease and cirrhosis, particularly in humans. Additionally, most of the reported CT techniques thus far require special techniques not yet available for daily clinical use, or extensive involvement by experienced radiologists.

Chen et al. [11] recently published on a statistical shape model (SSM) to diagnose and quantify cirrhotic livers from CT scans based on morphological analysis and machine

learning, using purely changes in liver and spleen shape, and reported classification approaches of 88 and 90 % for normal and abnormal livers, respectively. This approach required performing the segmentation of the liver and the spleen under the guidance of a physician in order to obtain accurate shapes. Another limitation was the use of subsets of the 44 training cases as the validation set instead of an entirely separate validation set.

Varenika et al. [12] recently published, using a mouse model, on using contrast-enhanced CT measurements of hepatic fractional extracellular space and macromolecular contrast material uptake to measure severity of liver fibrosis. Twenty-one rats received intragastric CCl₄ for 0–12 weeks followed by imaging with respiratory-gated micro CT, using both a conventional contrast material and a novel iodinated macromolecular contrast material. They reported correlations between CT measurements of fractional extracellular space and Ishak fibrosis score ($R^2=0.751$) and between CT measurements of macromolecular contrast material uptake and Ishak fibrosis score ($R^2=0.827$).

In a recently published retrospective case-control study, Zissen et al. [13] evaluated the use of contrast-enhanced CT quantification of the hepatic fractional extracellular space (ECS) with the severity of diffuse liver disease using 106 patients and measurements of the CT attenuation of the liver and aorta by an experienced radiologist and a trainee to estimate the fractional ECS, and reported correlation with the MELD score ($r=0.572$). The reported technique was predictive of cirrhosis with an AUROC of 0.953.

We have previously shown “proof of principle” that this can be achieved by quantifying the morphological features typically seen on CT scans of cirrhotic livers in a semi-automated method [14]. In our previous study, we only examined patients at the opposing spectrum of disease comparing CT scans of normal patients without any liver disease and patients with biopsy proven cirrhosis. Because the development of cirrhosis represents the endpoint of a spectrum of disease ranging from no fibrosis to fibrosis to cirrhosis and the clinical question is often posed whether a patient with pre-existing liver disease has developed cirrhosis, we sought to develop a predictive tool which is able to predict cirrhosis regardless of whether the patient has some degree of liver disease. In this study, we included in the “non-cirrhotic” group, not only patients who had completely normal livers without any evidence of chronic liver disease but also patients who had chronic liver disease where the presence of fibrosis ranged from no fibrosis to bridging fibrosis which is just short of cirrhosis. In addition, to examine whether cirrhosis was reported during routine radiological reading, we compared the findings by the predictive model to the actual radiology reports. Radiologic diagnosis of cirrhosis was made in a routine clinical practice in which many different radiologists interpret CT images.

Materials and Methods

Study Population

Stratified sampling design study was set up, and the cohort of cases was identified through cross referencing of pathology and radiological clinical databases. The database of liver biopsies from the University of Michigan during the period of January, 2004 to March, 2009 was cross referenced with the radiology database to identify cases where there was an abdominal CT scan for any reason within 6 months of the liver biopsy. All the clinical information for these patients were obtained from the electronic medical records and reviewed by 2 clinician/investigators. 130 CT scans were identified as suitable for this study because the scan contained the entire liver and there was no mass lesion which could alter the liver anatomy, no missing patient information such as height/weight, blood count or liver panel, or insufficient liver tissue for diagnosis. The 130 CT scans were from patients with a wide spectrum of liver disease including hepatitis C, nonalcoholic fatty liver disease, alcoholic fatty liver disease, autoimmune hepatitis, primary sclerosing cholangitis, alpha-1 anti-trypsin disease, hepatitis B, or cryptogenic. Of these, 51 had biopsy proven cirrhosis and the remainder had variable amounts of fibrosis. An additional 37 CT scans were identified by cross referencing the radiology database with the University of Michigan Trauma Registry from the period of March 2001 to August of 2009. Consecutive patients were identified who had CT scans within 6 months of the liver enzyme measurements. All the patients had normal liver enzymes and no evidence for liver disease by history, clinical or radiological exam within 6 months of the lab results. In addition, there was no missing patient information or insufficient scans.

The cases were then randomly divided into the training set ($n=88$) and the validation set ($n=79$). This study was approved by the Institutional Review Board at the University of Michigan.

Quantitative Image Analysis

Quantitative image analysis was performed as previously described [14].

Briefly, each liver was segmented using Mimics software (Materialise, Leuven, Belgium). At this time, manual segmentation is the best way to delineate the liver surface. When designing a new liver segmentation algorithm, the manual segmentation is used as a reference standard to assess the performance of automated or semi-automated segmentation. Again, it is important to stress here that the focus of this work was not development of another automated liver segmentation algorithm, which is a major area of research in and of itself [1]. The focus was development of CAD based on quantifying morphology using segmented livers, regardless of how they

were segmented. Mimics is a commonly used tool for 3D medical image processing.

The resulting liver surfaces were saved as stereolithography (STL) mesh objects into a spatially enabled Oracle database. The STL format describes the geometry of the liver in the form of unit normals and vertices. This is one of the universally acceptable ways of saving 3D surface geometry. These mesh objects were saved in an Oracle database along with the measures derived from this geometry. The Oracle database was then used to save and retrieve such geometry and measures in an organized and efficient manner.

Subsequently, the STL mesh and the Digital Imaging and Communications in Medicine (DICOM) files representing the raw CT data were loaded into MATLAB® software (MathWorks Inc., Natick, MA). For each liver, several parameters were evaluated for the entire liver surface as well as for five representative slices of each liver, defined as the slice with the left tip of the liver as well as two slices on either side. A bounding box defined as the smallest rectangular box which will fit the liver was created both for the whole liver (bounding box) and for each of the five slices. The bounding box is aligned with the three axes: X (lateral-medial), Y (anterior-posterior), and Z (craniocaudal). All the patients were scanned in the supine position. The X -axis is in the transverse plane, from the patient's right to left, the Y -axis moves from the rib cage to spine, and the Z -axis moves from head to toe. Clearly, there is positional variance of liver between different patients; however, one of the key goals of this research effort was to determine whether easily definable and computable parameters, such as using bounding boxes aligned with the 3 axes, are adequate for predictive model creation.

Multiple morphological markers were measured automatically using previously described MATLAB® algorithms [14]. Both the direct measurements as well as calculated ratios equalized to body surface area (BSA) were inputted into the model for analysis. Those measurements which did not involve the entire liver, but instead an easily identifiable set of slices of the liver, represent the averages over the five representative slices as described and defined above. In addition to direct and equalized measurements, other distinct measurements include:

Liver slice–bounding box slice ratio was calculated using the *entropy* function provided by MATLAB® using the equation: $-\sum_k ([p(l)] \times \log_2[p(l)])$ where the summation is across all the gray levels l of the image. $p(l)$ is the probability of the occurrence of the gray level l based on the image histogram technique. For the purposes of calculating this ratio using the *entropy* function, all the pixels outside the liver boundary were set to gray level value of 0. For a given three-dimensional liver object, imagine a slice that cuts through both the liver as well as the surrounding bounding box. In the resulting two-dimensional plane, there is now a representative liver slice

with its various gray levels as well as the surrounding bounding box slice, a rectangle. This calculated ratio then describes the way in which the liver slice fills that surrounding rectangle.

The parameter tortuosity was measured using the method described by Dougherty and Varro [15], where three-dimensional tortuosity index (TC_{3D}) was defined in terms of two-dimensional tortuosity indices in the X -axis (TC_X) and Y -axis (TC_Y) directions: $TC_{3D} = (TC_X^2 + TC_Y^2)^{1/2}$. TC_X and TC_Y are defined as the sums of the absolute values of the differences between successive X and Y coordinates, respectively, divided by the sampling interval p , which in this research was set as the length of the slice perimeter of the slice with the left tip divided by 75, a number chosen at random to partition the perimeter into multiple small segments.

The left tip curvature was calculated as a reciprocal of radius and radius in turn solved as a least mean squares problem using a set of five points spaced evenly around the left tip of the liver. Liver volume and surface area were obtained directly from the Oracle database with built-in

database functions. Liver slice perimeter and slice area were calculated using built-in MATLAB[®] routines. From the stack of CT slices, the representative five slices were chosen as detailed above. The average liver perimeter and the average liver area over these five slices were calculated for each liver.

Statistical Analyses

The statistical analyses were performed by using statistical software R (www.r-project.org). Assuming a patient with a set of morphologic features $M = (M_1, M_2, \dots, M_k)$, where k is the total number of morphologic features (26 for our study, listed both in Table 1 and Fig. 2), the logit of the probability of this patient having cirrhosis (denoted by p), is modeled as: $\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 M_{r1} + \beta_2 M_{r2} + \dots + \beta_j M_{rj}$.

The challenge is to identify the “predictive” features, $M_{r1}, M_{r2}, \dots, M_{rj}$, which can be utilized to build such models. Here, $M_{r1}, M_{r2}, \dots, M_{rj}$, is a subset of $M = (M_1, M_2, \dots, M_k)$, with at most eight predictive features.

Table 1 Univariate analysis of measured parameters: Mean values of each parameter for the two groups (non-cirrhotic, cirrhotic), with p values to show parameters that had statistically significant differences in the mean values

Measured parameter	Non-cirrhotic (mean $\pm$ STD)	Cirrhotic (mean $\pm$ STD)	p value
Liver slice–bounding box ratio	1.19 $\pm$ 0.18	1.02 $\pm$ 0.23	<0.0001*
Tortuosity	12.70 $\pm$ 1.59	13.55 $\pm$ 2.07	0.011*
Left tip curvature	0.05 $\pm$ 0.02	0.06 $\pm$ 0.02	0.012*
Bounding box X dimension	202.63 $\pm$ 25.88	217.44 $\pm$ 33.14	0.006*
Bounding box Y dimension	177.79 $\pm$ 23.28	184.14 $\pm$ 28.18	0.162
Bounding box Z dimension	166.55 $\pm$ 24.88	157.48 $\pm$ 32.81	0.082
Liver volume	1,767,059.94 $\pm$ 488,314.31	1,741,720.710 $\pm$ 696,253.84	0.814
Liver area	89,787.02 $\pm$ 16,456.71	92,099.40 $\pm$ 24,783.66	0.544
Slice perimeter	409.09 $\pm$ 76.27	459.27 $\pm$ 103.28	0.003*
Slice area	17,832.80 $\pm$ 4,612.28	17,488.60 $\pm$ 6303.19	0.727
Liver slice–bounding box X dimension/ Y dimension	1.27 $\pm$ 0.24	1.34 $\pm$ 0.23	0.065
Slice perimeter/BSA	218.32 $\pm$ 36.68	239.25 $\pm$ 36.38	0.001*
Slice area/BSA	9,523.83 $\pm$ 2357.04	9,089.69 $\pm$ 2,819.54	0.339
Slice perimeter/slice area	0.02 $\pm$ 0.00	0.07 $\pm$ 0.24	0.140
Liver volume/BSA	940,497.06 $\pm$ 238,599.42	900,384.23 $\pm$ 320,059.60	0.425
Liver volume/bounding box volume	0.29 $\pm$ 0.04	0.27 $\pm$ 0.04	0.0003*
Liver area/BSA	48,221.50 $\pm$ 9,529.74	48,046.58 $\pm$ 10,861.91	0.921
Bounding box X dimension/ Y dimension	1.16 $\pm$ 0.20	1.20 $\pm$ 0.23	0.229
Bounding box X dimension/ Z dimension	1.24 $\pm$ 0.21	1.43 $\pm$ 0.35	0.0004*
Bounding box Y dimension/ Z dimension	1.09 $\pm$ 0.19	1.20 $\pm$ 0.20	0.001*
Bounding box X dimension/BSA	109.72 $\pm$ 22.29	114.99 $\pm$ 19.78	0.130
Bounding box Y dimension/BSA	95.43 $\pm$ 14.58	96.90 $\pm$ 13.75	0.535
Bounding box Z dimension/BSA	89.94 $\pm$ 17.88	83.46 $\pm$ 19.68	0.047*
Bounding box X dimension/liver area	0.0023 $\pm$ 0.0003	0.0025 $\pm$ 0.0005	0.034*
Bounding box Y dimension/liver area	0.0020 $\pm$ 0.0003	0.0021 $\pm$ 0.0004	0.318
Bounding box Z dimension/liver area	0.0019 $\pm$ 0.0002	0.0018 $\pm$ 0.0003	0.013*

* $p < 0.05$

We did an exhaustive search of over 2.5 million models with any combination of at most eight morphologic features. This total number of over 2.5 million models is the result of the following calculation, given that the total number of morphologic features in this research was 26 (listed in Table 1 and Fig. 2):

$$\binom{26}{0} + \binom{26}{1} + \binom{26}{2} + \binom{26}{3} + \binom{26}{4} + \binom{26}{5} \\ + \binom{26}{6} + \binom{26}{7} + \binom{26}{8} = 2533987$$

Fig. 1 Stereolithography (STL) representation of non-cirrhotic (**a**) and cirrhotic (**b**) liver. In these 3D figures, *X*-axis is *left to right*, *Y*-axis *anterior to posterior*, and *Z*-axis *caudal to cranial*

To further illustrate the above concept with a simple example, let us assume we have four features in total (A, B, C, D), now, all models with at most two features are: Null model, A only, B only, C only, D only, (AB), (AC), (AD), (BC), (BD), and (CD).

We fitted logistic regressions with all possible configurations up to eight predictors. These models were then ranked by Akaike information criterion (AIC). We selected the top 100 models based on this ranking. The coefficients of the final prediction model were averages of coefficients of these top 100 models weighted by AIC. The detail of algorithm is described in the cited

reference [16]. Statistical inferences are based on either one of selected models, or averaging of all selected models which has the advantage of addressing the model uncertainty and variance [16].

Results

Quantitative Analysis of the Liver Morphology in Cirrhosis

By segmenting the livers and storing them as STL mesh objects in a spatially enabled database, we were able to quantitate the three-dimensional characteristics of the liver as captured by the CT scan. In Fig. 1, we show representations of the STL mesh objects for a typical non-cirrhotic liver (Fig. 1a) and cirrhotic liver (Fig. 1b). Cirrhotic livers develop characteristic shape distortions which are distinct from non-cirrhotic livers. They appear to have smaller fill-in ratios than non-cirrhotic livers, demonstrated by the ratio liver volume/bounding box volume. Because of the shape distortion with larger X and Y dimensions but smaller Z dimensions, a cirrhotic liver may

actually require a larger bounding box than a non-cirrhotic liver. Thus, we hypothesized that quantitation of the morphologic changes may be helpful in predicting cirrhosis. We measured 26 morphologic features of cirrhotic and non-cirrhotic livers and found significant differences between the two groups as noted on univariate analysis (Table 1 and Fig. 2). These changes reflect quantitative change in liver shape proportional to the bounding box and also the change in liver shape as demonstrated by bounding box dimensional changes.

Development of Predictive Models for Cirrhosis

Using these features, we then developed models to predict cirrhosis. The best model for predicting cirrhosis in terms of AIC is shown in the first row of Table 2. With this model, we calculated an AUC of 0.89 for the training set and 0.85 for the validation set. The next four selected models according to their AUC performance are listed thereafter on Table 2. Finally, we also averaged all top 100 selected models, where the method of weighting different models is based on

Fig. 2 Frequencies of presence of specific morphologic parameters in 100 best models (by Akaike information criterion (AIC))

Table 2 AIC and AUC values for the training set and validation set for selected models; with models specified by the parameters they contain

Selected model	AIC	Number of parameters utilized	Parameters	AUC training set ($n=88$)	AUC Verify Set ($n=79$)
1	84.16	8	Liver slice–bounding box slice ratio, bounding box Y dimension, liver volume, slice perimeter/BSA, liver volume/bounding box volume, bounding box Y dimension/ Z dimension, bounding box X dimension/BSA, bounding box Z dimension/BSA	0.89	0.85
2	84.24	6	Liver slice–bounding box slice ratio, liver volume, slice perimeter, liver area/BSA, bounding box X dimension/BSA, bounding box X dimension/liver area	0.86	0.85
3	84.46	8	Liver slice–bounding box slice ratio, bounding box Y dimension, slice perimeter, liver volume/BSA, liver volume/bounding box volume, bounding box Y dimension/ Z dimension, bounding box X dimension/BSA, bounding box Z dimension/BSA	0.89	0.84
4	84.73	8	Liver slice–bounding box slice ratio, bounding box Y dimension, liver volume, slice perimeter, liver volume/bounding box volume, bounding box Y dimension/ Z dimension, bounding box X dimension/BSA, bounding box Z dimension/BSA	0.89	0.85
5	84.94	7	Liver slice–bounding box slice ratio, bounding box Y dimension, slice perimeter/BSA, liver volume/BSA, liver volume/bounding box volume, bounding box Y dimension/ Z dimension, bounding box X dimension/BSA	0.88	0.84
Average of top 100 selected models	N/A	N/A	N/A	0.88	0.87

Buckland et al. [17]. The AUC performance for model averaging was 0.88 and 0.87 for training set and validation set respectively (Table 2)

We ranked all the morphological features by the frequency of occurrence in our top 100 models (Fig. 2). We found that two morphologic features, the liver slice–bounding box slice ratio and bounding box X dimension/BSA were found in almost all selected models. In addition, other important features included the liver volume/bounding box volume, slice perimeter, liver area/BSA, and bounding box X dimension/liver area.

Comparison to Radiology Reports

First, we first examined the radiology reports of the 167 CT scans to determine if the diagnosis of “cirrhosis” was reported and compared this to the biopsy results. Three confusion

matrices are provided to illustrate the comparisons to radiology reports (Tables 3, 4, and 5). Table 3 demonstrates the sensitivity and specificity of reporting “cirrhosis”. Of the 51 cases of biopsy proven cirrhosis, only 23/51 had the diagnosis of cirrhosis on the radiology report (sensitivity 0.45). By contrast, of 116 non-cirrhotic livers, only 1 was incorrectly reported as “cirrhosis” (specificity 0.99).

To determine the utility of our CAD, we utilized two different thresholds for giving the diagnosis of cirrhosis, and the average of our top 100 models as our aggregate predictive model. In Table 4, using a threshold with the highest accuracy, nine more cases of cirrhosis would have been picked up by the CAD, in addition to the 23 cases already read out by the radiologist, increasing the sensitivity to 0.63. However, with this threshold, the number of false positive would have increased by three, reducing the specificity to 0.97—if the

Table 3 Accuracy of radiological reading of cirrhosis

Radiologist read	Pathologic diagnosis (reference)	
	Cirrhosis	Non-cirrhotic
Cirrhosis	23	1
No cirrhosis	28	115

Accuracy=0.83 (95 % CI 0.76–0.88), Sensitivity=0.45, Specificity=0.99, Pos Pred Value=0.96, Neg Pred Value=0.80

Table 4 Three-way comparison between biopsy, radiology reads; using the CAD method optimized for best overall accuracy

Radiologist reading	Pathologic diagnosis: cirrhotic	
	CAD = cirrhosis	CAD = non-cirrhotic
Cirrhosis	15	8
No cirrhosis	9	19
Radiologist reading	Pathologic diagnosis: non-cirrhotic	
	CAD = cirrhosis	CAD = non-cirrhotic
Cirrhosis	1	0
No cirrhosis	3	112

Table 5 Three-way comparison between biopsy, radiology reads; using the CAD method with the greatest sensitivity

Radiologist reading	Pathologic diagnosis: cirrhosis	
	CAD = cirrhosis	CAD = normal
Cirrhosis	20	3
Normal	24	4
Radiologist reading	Pathologic diagnosis: non-cirrhotic	
	CAD = cirrhosis	CAD = normal
Cirrhosis	1	0
Normal	26	89

radiologist had agreed with the CAD reading. In Table 5, using a threshold with the highest sensitivity, utilization of the CAD method would have picked up an additional 24 cases of cirrhosis, with the overall sensitivity increased to 0.92. However, this would have brought the number of false positives to 26 and decreased specificity to 0.77—again, if the radiologist had agreed with the CAD reading.

Discussion

In this study, we have demonstrated that by segmenting the livers from incidental CT scans and storing the digital data in a spatially oriented database, we can quantify the morphometric features which characterize cirrhosis. This methodology, coined by us as “analytic morphomics” [18–20], provides additional objective information to assist radiologists during the interpretation of CT scans to make the diagnosis of cirrhosis. In clinical practice, it may be utilized to develop a CAD method to improve the sensitivity of cirrhosis diagnosis by radiologists.

In this study, we examined both patients with normal livers as well as patients with chronic liver disease, and found that analytic morphomics were able to differentiate cirrhosis with reasonable accuracy even in this more challenging population. This is important from a clinical standpoint as often the question of whether or not cirrhosis is present is asked in patients who have pre-existing liver disease such as hepatitis C. Although the liver biopsy remains the gold standard for making the diagnosis of cirrhosis, this is often not done in clinical practice given the risks of biopsy, with up to 55 % of primary care providers reporting patient refusal of liver biopsy [21]. Often the diagnosis of cirrhosis is not made by biopsy or by physical exam but by laboratory testing and imaging [22]. Imaging is more accurate in making the diagnosis of cirrhosis than physical exam [23]. Yet as noted in our study, the relative sensitivity of reporting cirrhosis is low at 45 % but with very high specificity of 99 % suggesting that radiologists are

conservative in reporting cirrhosis. With this in mind, we chose thresholds to examine whether a CAD method could improve the sensitivity of detecting cirrhosis and noted that if accuracy were preserved, we could increase the sensitivity of cirrhosis diagnosis to 63 % with little loss of specificity.

Because we only utilized incidental scans which were not performed with any specific protocol, we based all of our measurements on shape changes. As expected, with cirrhosis there is increased nodularity of the liver which is reflected in the increased tortuosity and slice perimeter. As there is shrinkage of the liver, the ratio of the liver to the bounding box significantly decreases. What is perhaps not as well appreciated is that while the liver shrinks, it also distorts resulting in an increase in the *X* and *Y* dimensions and decrease in *Z* dimension. In essence, the liver flattens out. The dimensional changes include caudate lobe hypertrophy and segmental hypertrophy in the lateral segments (II, III) of the left lobe, and segmental atrophy of both the posterior segments (VI, VII) of the right lobe and medial segment (IV) of the left lobe. In our analysis, we were able to detect these changes by containing the liver within a bounding box and measuring dimensional ratios [24]. Overall, these changes result in an increase in the bounding box volume. While calculation of liver volume is common, this calculation by itself is not sufficient to predict cirrhosis [25].

Limitations of our research include use of liver biopsy as the gold standard for diagnosis of cirrhosis, given that liver biopsy suffers from sampling error and inter-observer discrepancy as discussed in the introduction. Additionally, regarding comparisons to radiology reports, the radiologic diagnosis of cirrhosis was made in a routine clinical practice in which many different radiologists interpret CT images. Therefore, the issue of inter- or intra-observer variability cannot be avoidable in this setting either. Also, by using the radiology reports in which radiologists were not specifically asked whether the liver is cirrhotic there is a possible bias of underreporting, in other words radiologist did not consider cirrhosis while reviewing the scan. This may explain the low sensitivity and the high specificity. A limitation of this research also results from using incidental scans which means livers are segmented with their vascular trees in them; it is possible inclusion/exclusion of large vessels may affect the results of the area or volume of the liver.

Although the disadvantage of utilizing incidental scans was that we were unable to utilize measures of textural changes to our model, the advantage is that we were able to use scans where the information regarding the liver was already present and just not reported. In summary, our CAD method is highly accurate in diagnosis of cirrhosis, functions along the full spectrum of liver disease, and may be utilized to provide additional information for radiologists in making the important diagnosis of cirrhosis.

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