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Use of Analytic Morphomics of Liver, Spleen, and Body Composition to Identify Patients at Risk for Cirrhosis

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Abstract

Background & Aims—A diagnosis of cirrhosis can be made on the basis of findings from imaging studies, but these are subjective. Analytic morphomics uses computational image processing algorithms to provide precise and detailed measurements of organs and body tissues. We investigated whether morphomic parameters can be used to identify patients with cirrhosis.

Methods—In a retrospective study, we performed analytic morphomics on data collected from 357 patients evaluated at the University of Michigan from 2004 to 2012 who had a liver biopsy within 6 months of a computed tomography scan for any reason. We used logistic regression with elastic net regularization and cross-validation to develop predictive models for cirrhosis, within 80% randomly selected internal training set. The other 20% data were used as internal test set to ensure that model overfitting did not occur. In validation studies, we tested the performance of our models on an external cohort of patients from a different health system.

Results—Our predictive models, which were based on analytic morphomics and demographics (morphomics model) or analytic morphomics, demographics, and laboratory studies (full model), identified patients with cirrhosis with area under the receiver operating characteristic curve (AUROC) values of 0.91 and 0.90, respectively, compared with 0.69, 0.77, and 0.76 for aspartate aminotransferase-to-platelet ratio, Lok Score, and FIB-4, respectively, by using the same data set. In the validation set, our morphomics model identified patients who developed cirrhosis with AUROC value of 0.97, and the full model identified them with AUROC value of 0.90.

Conflicts of interest

These authors disclose the following: S.C.W. and G.L.S. have 2 patents pending regarding technology described in this article. The remaining authors disclose no conflicts.

Conclusions—We used analytic morphomics to demonstrate that cirrhosis can be objectively quantified by using medical imaging. In a retrospective analysis of multi-protocol scans, we found that it is possible to identify patients who have cirrhosis on the basis of analyses of preexisting scans, without significant additional risk or cost.

Keywords

Prognostic; FactorNoninvasive; MarkersAdvanced; TechnologyFibrosis; Progression

The diagnosis of cirrhosis represents an important clinical landmark in the care of patients with chronic liver disease.¹ The gold standard for making the diagnosis of cirrhosis is a liver biopsy; however, in clinical practice, this is not practical because of the inherent risks associated with a biopsy. The diagnosis is routinely made by history, physical exam, and laboratory findings, but radiologic imaging is rapidly becoming more important as the quality of medical imaging technologies improve. With development of cirrhosis, many changes in the shape of the liver can be seen radiologically.² In addition, there are associated changes of portal hypertension, such as splenomegaly and abdominal varices, that can help radiologists make the diagnosis of cirrhosis. Although these qualitative changes are helpful, the ability to visually detect them occurs only with the most advanced disease, thus limiting their utility in the detection of early cirrhosis. Furthermore, there are other clinically important alterations in body composition (such as changes in bone metabolism, fat distribution, muscle quality, and soft tissue) associated with advanced liver disease and cirrhosis that are not easily captured by a qualitative read and may be important in making the diagnosis.³ For example, cirrhosis is also associated with diminished muscle mass, and we and others have shown that quantitation of this sarcopenia can predict prognosis as well as outcome after transplantation in patients with cirrhosis.^{4, 5, 6, 7}

We hypothesize that changes in body composition can be quantitated to objectively predict cirrhosis. Analytic morphomics is a novel methodology that can accurately assess and quantify body composition by using computed tomography (CT) scans. The aim of this study was to determine whether analytic morphomics can be used to predict cirrhosis. With this in mind, we applied analytic morphomics to analyze a retrospective cohort of patients with chronic liver disease at the University of Michigan who had paired biopsies and CT scans for multiple reasons. We used these measurements to build predictive models. We then validated the models by using an internal test set and on an external cohort of patients with similar paired biopsy and CT at the Veterans Affairs Ann Arbor Healthcare System (VAAHS).

Methods

University of Michigan Study Population (University of Michigan Cohort-Development and Internal Test Cohort) and Veterans Affairs Ann Arbor Healthcare System (External Test Cohort)

The University of Michigan cohort was identified through cross-referencing of pathology and radiologic clinical databases. This study was approved by the Institutional Review Board at the University of Michigan and the VAAHS. Two thousand one hundred sixty-six

patients were identified as having had both a liver biopsy and a CT scan within 6 months of each other at the University of Michigan from January 2004 to March 2012. Of these, 399 patients had scans that were de-identified and downloaded into the Morphomics server. The remainder of these patients were excluded because the biopsies did not include liver tissue because most of the patients had biopsies for metastatic or primary liver cancer, the scans only included the chest and not abdomen, the patient was post liver resection, and/or the scans were not available for download (usually because they were consultation scans that were not loaded into the system). Of the 399 scans that were processed, 25 scans were excluded because age of the patient was younger than 16 at the time of the study, and 17 were excluded because the scan was of poor quality or did not include the entire liver, spleen, or all measurable morphomics features. Only 1 scan had portal vein thrombosis, and this did not significantly affect spleen morphomics. All the clinical information for these patients was obtained from the electronic medical records and reviewed by a hepatologist (G.L.S). Only 1 CT scan was used per patient, and this was the scan closest to the biopsy date. Laboratory data obtained were within 6 months of the CT scans.

The external test cohort was obtained by cross-referencing the pathology and radiologic clinical database at the VAAHS. All patients who had a liver biopsy at the VAAHS from January 1, 2005 to March 1, 2010 and a CT scan for any reason within 6 months of the liver biopsy were considered. One hundred patients were identified. Of these, 38 scans were retrieved, de-identified, and processed. The remainder of the patients were not considered for similar reasons as stated above for the University of Michigan cohort (ie, no liver tissue, post liver resection, etc). One scan was excluded because the patient was lying on his side, and we could not accurately anatomically index the spine.

Analytic Morphomics

The general methodology of analytic morphomics has been previously described by our group.^{2, 8, 9, 10} Briefly, de-identified Digital Imaging and Communications in Medicine (DICOM) files of the CT scans were loaded into the analytic morphomics server. Image processing and analysis were performed by using a semiautomated high throughput methodology with algorithms programmed in MATLAB (MathWorks Inc, Natick, MA). All the algorithms involved a combination of user-defined points followed by automated processing and concluded with user editing and verification. The initial processing step was the semiautomated identification of the spinal vertebral levels, which then served as the anatomic reference system for subsequent analysis (Figure 1A). The rationale for this “anatomic indexing” was to allow for precise measurements standardized for each individual. For example, if we wanted to look at a slice at the bottom of third lumbar vertebra, this could be accurately retrieved for each individual. After the anatomic indexing, we then identified the fascial envelope and skin outline. This was done automatically after the user was asked to define key points within the linea alba at specified vertebral points (Figure 1B). The dorsal muscle groups were also defined automatically after the user delineated the paraspinus lateral seams at specified vertebra points (Figure 1C). For the identification and segmentation of the liver and spleen, which were more complex structures, we used a 2-step semiautomated method. In the first step the user was asked to define the outer borders at particular points in 3 different views (axial, sagittal, and coronal). The

information was analyzed by the computer automatically, and a proposed outline of the organ was generated that could then be edited by the user (Figure 1D). For more technical information regarding the MATLAB algorithms, see Supplementary Methods. Processing of the scans was performed by trained research assistants. Proficiency in the processing was usually achieved after 6–12 hours of training. The manual user time to process and edit was approximately 40–60 minutes per scan, depending on the quality of the scan and skill of the research assistant. For quality assurance, each de-identified scan was further visualized by another researcher to ensure that the outlines of organs and components were correct.

The liver and spleen geometries were then saved in a stereolithography format in the analytic morphomics database with Oracle Spatial data option (Oracle Corp, Redwood City, CA). These geometries were then subsequently retrieved to calculate several shape-and pixel-based measurements. For detailed descriptions of the measurements, see Supplementary Methods.

Calculation of Serum Fibrosis Markers

Three well-established scoring systems for predicting cirrhosis by using standard laboratory values were calculated as previously described.^{11, 12} Aspartate aminotransferase (AST) (AST-to-platelet ratio index [APRI]) formula: $[\text{AST} (\times \text{upper limit of normal})/\text{platelet} (109/\text{L})] \times 100$; FIB-4 score formula:

$$\frac{\text{age}(\text{years}) \times \text{AST}(\text{U/L})}{\text{platelet} (109/\text{L}) \times \sqrt{\text{alanineaminotransferase (ALT)}(\text{U/L})};$$

Lok Score¹²: $\text{Log odds (predicting cirrhosis)} = -5.56 - 0.0089 \times \text{platelet} (\times 103/\text{mm}^3) + 1.26 \times \text{AST/ALT ratio} + 5.27 \times \text{international normalized ratio}$. The values for the upper limit of normal for AST were set according to the International Federation of Clinical Chemistry, that is, 35 U/L for men and 30 U/L for women. The values used for the upper limit of normal for ALT were 19 U/L in women and 30 U/L in men.¹¹

Statistical Analyses

Descriptive analyses were conducted to examine group differences between patients who had liver cirrhosis versus those who do not. Summary statistics were computed for continuous measures as mean $\pm$ standard deviation or median (interquartile range [IQR]) if the distribution was skewed and for categorical variables as frequency and proportion (%). Variables were assessed for normality, and log-transformation was applied if necessary. The Kolmogorov–Smirnov test was used to test for normality. Two sample t tests was used for comparison of normally distributed continuous variables between groups, the Wilcoxon–Mann–Whitney test was used for comparison of continuous variables that had skewed distribution between groups, and the Fisher exact test was used for comparison of proportions. We used logistic regression models to evaluate the prediction ability of covariates of interest for the risk of having liver cirrhosis. Appropriate variable selection procedure, such as the elastic net regularization used as a penalty for model complexity, was used to leverage between prediction ability and model overfitting. Such a balance was controlled by tuning parameters to achieve the optimization through 10-fold cross-

validation. Area under receiver operating characteristic curve (AUROC) was computed to compare performance of different models. The final models were refitted with all the samples in University of Michigan data set or VAAHS data set and used to calculate AUROC for comparisons. All statistical analyses were performed by using R 2.15.2 and the package, glmnet (<http://www.jstatsoft.org/v33/i01/>). To make statistical inferences, P values <.05 were considered as statistically significant.

Results

Descriptive Analysis of the Cohort Between Cirrhosis Group and Non-cirrhosis Group

In Table 1 we summarized the descriptive statistics of all demographic variables and laboratory measurements for both cirrhosis patients and the non-cirrhosis patients in our study cohort. In the study cohort, 164 patients were female, and 193 were male. One hundred had biopsy-proven cirrhosis, and 257 were non-cirrhotic. One hundred twenty-six patients had hepatitis C virus, 90 patients had nonalcoholic fatty liver disease (NAFLD), or 141 had other liver diagnosis including 39 who had normal liver and the remainder with chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and alcohol. Two hundred eighty-five patients still had their native livers, and 72 were post liver transplant. In comparing the patients in the cirrhotic cohort with those from the non-cirrhotic cohort, there was no difference in gender or ALT levels. However, the cirrhotic patients were slightly older than the non-cirrhotic patients (52.1 ± 12.7 vs 48.6 ± 13.2 years), and there were differences in the distribution of diagnosis on univariate analysis likely related to reasons for obtaining the biopsy. However, on multivariate logistic regression analysis, diagnosis was not a significant predictor for cirrhosis. Not surprising, there was also a significant difference between the cirrhotic and non-cirrhotic populations in regard to laboratory values and previously described serum fibrosis markers including AST, platelet, Model for End-Stage Liver Disease (MELD), APRI, Lok Score, and FIB-4.

Developing Predictive Models for Cirrhosis

To build a predictive model for cirrhosis, we randomly divided the University of Michigan cohort into training (80%) and internal test sets (20%). Within the 80% randomly selected training set, we optimized tuning parameters through 10-fold cross-validation. The other 20% of data was used as an internal test set to ensure no model overfitting. We developed 3 different models in which we included different variables. In all the models, we included demographic variables such as age, gender, diagnosis, and transplant status because these may have potential to affect body composition. In the first model (Liver and Spleen Morphomics), we included variables that measured the geometry of the liver and spleen. These are described in greater detail in Supplementary Methods. A brief description of some of the important variables is pictorially illustrated. These include measurements such as the bounding box around the liver and spleen either in the original orientation of the patient lying on the CT scanner (Figure 2A) or reoriented (Figure 2B) to find the smallest possible volume. The bounding box is defined as the smallest possible 3-dimensional rectangular box that can contain the organ of interest.² Another set of measurements included were surrogates of the caudate-to-right-lobe ratio that has previously been shown to be predictive

of cirrhosis.¹³ By having a user define the bifurcation of the main portal vein, we can measure the distance between that point and the right most lateral surface of the liver. This distance measures the relative size of the right lobe of the liver (Figure 2C). By defining the lateral surface of the caudate lobe, you can then measure the relative size of the caudate lobe (Figure 2C). By defining the fascial and skin outlines, we can determine the relative body sizes of each individual. The distance from the anterior surface of the spine to the anterior fascia (Figure 2D) can be a surrogate of body size, and the height of the vertebra can a surrogate for a patient's height.

In the second model (All Morphomics), we included everything from the Liver and Spleen Morphomics as well as measurements of other features within the abdominal cavity such as bone dimensions and density, muscle mass, and other soft tissue characteristics as previously described.^{6, 8, 9, 10, 14, 15} In the third model (All Morphomics and Labs), we included All Morphomics measurements as well as laboratory data.

To identify the final predictors for each model, we fitted a logistic regression model for the probability of having cirrhosis by using the training set. We denoted the initial predictors (variables) as $M_1, M_2, \dots, M_k$, where k was the total number of features we were considering. Let Y_i denote whether subject i had cirrhosis or not and where $i=1, 2, \dots, n$; then we fitted the following logistic regression

model: $\text{logit}(P[Y_i=1|M_{i,1}, M_{i,2}, \dots, M_{i,k}]) = \beta_0 + \beta_1 M_{i,1} + \beta_2 M_{i,2} + \dots + \beta_k M_{i,k}$, where $\text{logit}(x) = \log(x/1-x)$. To select the important predicative features while keeping the model parsimonious, we applied an elastic net penalty term to balance between model accuracy and model complexity. Specifically, we estimated the parameters by minimizing $\sum_{i=1}^n \ln(\beta_0, \beta_1, \dots, \beta_k | Y_i, M_{i,1}, M_{i,2}, \dots, M_{i,k}) + \gamma \{ \alpha \sum_{j=1}^k |\beta_j| + (1-\alpha) \sum_{j=1}^k (\beta_j)^2 \}$ where the first term stands for goodness of fit for the regression model to the data ($\ln(\cdot)$ is the log-likelihood function for one single observation), and the second term stands for penalty for model complexity. γ is the tuning parameter to control the balance between these two, and α is the tuning parameter to control the contribution between L^1 and L^2 penalties. We choose the tuning parameter γ and α by using 10-fold cross-validation.

The final selected variables and regression coefficients (β) for each predictive model are shown in Supplementary Table 1. We found that transplant status was an important variable in all the models. This is not surprising because many of the changes in body composition that occur with cirrhosis (such as splenomegaly) do not resolve even after a patient receives a liver transplant. In addition, the measurements based on caudate-to-right-lobe ratio were also important predictors of cirrhosis, supporting prior studies characterizing this change during the development of cirrhosis. With each model, we calculated AUROC for the training and internal test sets (Table 2).

To further examine the validity of our models to function independently in a different population, we tested their predictive ability on a small external test set of patients from an entirely different health care system, the VAAHS. In this cohort, we had 37 patients (34 male/3 female) of whom 8 patients had biopsy-proven cirrhosis and 29 patients did not. Thirty-four had not had a liver transplant, and 3 patients were post liver transplant. Twenty-

four patients had hepatitis C virus, 6 patients had NAFLD, and 7 patients had other liver diagnosis.

By using this external cohort of scans from the VAAHS, we tested our predictive models and found that they performed with similar accuracy. Our AUROC was 0.92, 0.97, and 0.90 for predicting cirrhosis by using Liver and Spleen Morphomics, All Morphomics, and All Morphomics with Labs, respectively (Table 2).

As a comparison to standard laboratory-based models, we used the entire University of Michigan cohort and calculated AUROC for our predictive models and compared them with the AUROC of the standard laboratory-based models, APRI, Lok Score, and FIB-4, which are 0.69 (CI, 0.63–0.75), 0.77 (CI, 0.71–0.82), and 0.76 (CI, 0.71–0.82), respectively (Figure 3).

A Single Slice Prediction Model

Because segmentation of the liver represented one of the most time-consuming and technically challenging aspects within our current process of analyzing the scans, we sought to decrease processing time by developing predictive models that did not require three-dimensional segmentation of the liver. Rather, we chose the slice of the liver at the bifurcation of the main portal vein and used measurements of the liver only at this slice. The rationale for this was that our prior finding suggested that variables that were surrogates for the caudate-to-right-lobe ratio were important predictors of cirrhosis, and thus measurements at this slice would continue to include this variable. By using measurements only at this slice and morphomics measurements, we were able to develop a very robust predictive model with AUROC of 0.91, 0.89, and 0.83 for the training, internal test, and external test sets, respectively (Table 2). By using the single liver slice measurements, body morphomics measurements, plus laboratory data, we found AUROC of 0.88, 0.96, and 0.92 for the training, internal test, and external test sets, respectively, supporting the feasibility of this approach. The variables in the final models were tabulated in Supplementary Table 2.

Discussion

In this study, we found that by using analytic morphomics to quantify body composition and geometry in CT scans, we were able to build models that can accurately predict cirrhosis. Very importantly, our study population comprised a broad spectrum of liver diseases, and the scans we used were obtained for a variety of clinical indications and performed by using different scanning protocols. We used 3 different approaches examining the predictive ability of measuring (1) only liver and spleen morphomics, (2) all morphomics, and (3) all morphomics plus laboratory values. With these 3 approaches, we found high AUROC for predicting cirrhosis. In all the models, we found that transplant status was very important. This is not surprising because the signs of portal hypertension in imaging studies do not regress after liver transplantation.¹⁶ However, the fact that our model was able to perform well even in patients who have had prior liver transplantation is of particular importance because this is a difficult clinical population in which to noninvasively predict cirrhosis. Many of the qualitative signs such as splenomegaly and abdominal varices routinely used by radiologists and clinicians to diagnose cirrhosis are no longer useful after liver

transplantation, and making the diagnosis without a biopsy is very challenging. Laboratory findings are also less valuable because many patients after liver transplantation continue to have thrombocytopenia despite a normally functioning liver.^{17, 18} In addition to the importance of knowing transplant status, we found that the relative distance of portal vein to caudate lobe was also another important predictor for cirrhosis because it was found in all the models. This is consistent with previous finding showing that enlargement of the caudate lobe is a marker of cirrhosis.¹³

Although we did not include standard morphomic measurements (ie, measurements of bone, muscle, fat, and interstitial tissue) in our first model (Liver and Spleen model), we found that it was important to index our liver and spleen measurements to the patients' morphomic size (ie, vertebral height or vertebra to fascial distance). There is a strong correlation of vertebral height to patient height as well as vertebral to fascial distance to abdominal circumference as measured on the CT scan, and we used these measurements as surrogates for overall patient size. We found that for measurements of liver and spleen size, indexing them to patient size was important. This is perhaps not surprising because sizes of individual organs are proportional to patient size.¹⁹ Having the ability to index the patient size by using measurements found on the CT scan is very practical. The alternative would be to input measures of height, weight, and body mass index, which are fraught with potential inaccuracies, particularly in a retrospective study. In addition, we have found that analytic morphomics can provide more precise measurements of body dimensions than standard measurements, which do not account for the population heterogeneity with regard to body shapes.^{20, 21}

The finding that liver measurements are important in predicting cirrhosis is consistent with our prior findings that liver shape and contour changes develop during disease progression to cirrhosis. With regard to spleen measurements, there is little information published about whether spleen shape can change with cirrhosis, although overall enlargement, splenomegaly, is a known sequela of cirrhosis. Multiple methods have been used to measure spleen size, but there is no accepted standard practice.²² We measured standard X, Y, and Z measurements of size and volume of the spleen in addition to other parameters such as eccentricity and perimeter, which are more indicative of shape changes. Many of the spleen measurements were important for predicting cirrhosis, but whether this is a reflection of change in spleen size as opposed to spleen shape will require more investigation.

Although the finding that liver and spleen measures are important for predicting cirrhosis is not surprising, the finding that other morphomics measurements may be important is novel. We found that interstitial tissue density is an important variable predictive of cirrhosis in our Morphomics model. The rationale for this finding is not entirely clear, but we hypothesize that interstitial tissue density may be a reflection of early portal hypertension. We are actively pursuing this hypothesis.

We sought to develop models that contained both radiologic and laboratory data because this could easily have clinical applicability. Of all the different laboratory-based studies, we found that the Lok Score was most predictive in our final model. This suggests that the combination of a few morphomics variables with laboratory-based calculation (the Lok

Score) can be used to accurately predict cirrhosis. In addition to the standard models where we segmented the entire liver, we also developed models that did not require three-dimensional segmentation of the liver. The rationale was to decrease processing time and increase the high throughput nature of our technique. To this end, we chose a single slice approach to analyzing the liver. We used the slice of the CT scan that was at the level of the bifurcation of the main portal vein because this would allow us to have the important measurement of portal vein to caudate distance ratio. We found that by using this simplified analysis of the CT image with and without laboratory data, we were still able to develop very robust predictive models for cirrhosis, while achieving substantial savings in cost and also improving ease of use.

Although our models performed well against the standard laboratory-based studies such as the APRI, Lok Score, and FIB-4, we were unable to compare it with FibroScan or other proprietary-based serum fibrosis markers (such as Fibrotest) because our study was retrospective, and we did not have those data points. Although the retrospective nature of our study may seem to be a weakness, it demonstrates that this approach can be used on preexisting data. Unlike other serum-based markers that are dependent on degradable biological samples, CT scans are unique in that the data files are stored in pristine fashion, and serial measurements by using the same original samples are possible. By creating a method that is not dependent on protocol-specific CT scans, we are able to derive important information from preexisting scans. From the perspective of epidemiologic and health services research, this methodology has tremendous potential. Our approach allows for retrieval of numerous patient-specific as well as precise and objective measurements in medical records beyond text searching, International Classification of Diseases, Ninth Revision codes, and laboratory values. With linkages to clinical records, there is significant potential in deriving valuable information from already available medical records. From a clinical perspective, this significantly decreases cost and does not require radiation exposure for the patient. DICOM data files can easily be uploaded from remote sites, and thus this analytic morphomics could have significant advantages for community practices or rural sites where access to technology such as Fibroscan may not be feasible.

To demonstrate the feasibility and general applicability of our methods, we obtained the DICOM files of CT scans from a different healthcare system, the VAAHS. We found that our model performed well on this external test set despite intrinsic differences in the scanning equipment used and patient populations. Although the numbers were small and will require further study and development of prospective studies, our results suggest that this methodology has significant promise as a technique that can be used for broad dissemination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
AST	aspartate aminotransferase
AUROC	area under the receiver operating characteristic curve
CI	confidence interval
CT	computed tomography
DICOM	Digital Imaging and Communications in Medicine
GUI	graphical user interface
IQR	interquartile range
MELD	Model for End-Stage Liver Disease
NAFLD	nonalcoholic fatty liver disease
VAAAHS	Veterans Affairs Ann Arbor Healthcare System

Appendix

Variable Dictionary for Liver and Spleen Features

- **LIVERVOLUME_MM3**: Total liver volume in MM3
- **LIVERAREA_MM2**: Total surface area of liver volume in MM2
- **LIVERINSPHERERADIUS**: Radius of a best-fit sphere inscribed within the liver in MM
- **LIVERBBOX_XLENGTH**: X length of the liver bounding box (not reoriented) in MM
- **LIVERBBOX_YLENGTH**: Y length of the liver bounding box (not reoriented) in MM
- **LIVERBBOX_ZLENGTH**: Z length of the liver bounding box (not reoriented) in MM
- **LIVERMINBBOX_X**: X length of a best-fit bounding box of the liver (reoriented) in MM
- **LIVERMINBBOX_Y**: Y length of a best-fit bounding box of the liver (reoriented) in MM

- LIVERMINBBOXZ: Z length of a best-fit bounding box of the liver (reoriented) in MM
- LIVERMINBBOXVOLUME: Bounding box volume of the best-fit bounding box in MM3
- LIVERMINBBOXAREA: Bounding box surface area of the best-fit bounding box
- LIVERMINBBOXEDGELENGTH: Bounding box perimeter of the best-fit bounding box in MM
- LIVERVOLUME_MINBBOXVOL_RATIO: Ratio of the minimum bounding box volume and liver volume(reoriented)
- LIVERVOLUME_BBOXVOLUME_RATIO: Ratio of the regular bounding box volume and liver volume
- LIVERBBOXVOLUME: Liver bounding box (not oriented) volume in MM3
- LIVERCIRCUMELLIPSE_XRADIUS: X radius of a best-fit superscribed ellipse over the liver in MM
- LIVERCIRCUMELLIPSE_YRADIUS: Y radius of a best-fit superscribed ellipse over the liver in MM
- LIVERCIRCUMELLIPSE_ZRADIUS: Z radius of a best-fit superscribed ellipse over the liver in MM
- LATERAL2PORTBIFURPT_XLENMM: X axis length (not shortest distance) between the lateral most liver point and the portal vein bifurcation point in MM
- PORTBIFURPT2CAUDATE_XLENMM: X axis length (not shortest distance) between the caudate lobe and the portal vein bifurcation point in MM
- C_RL_RATIO_BIFURPT: Ratio between LATERAL2PORTBIFURPT_XLENMM and PORTBIFURPT2CAUDATE_XLENMM
- MEANLIVERHU: Mean liver Hounsfield units of the liver
- LIVERBBOXAREA: Liver bounding box area (not oriented) in MM2
- LIVERMINBBOX_ZX_RATIO: Ratio between LIVERMINBBOXZ and LIVERMINBBOXX
- LIVERMINBBOX_YZ_RATIO: Ratio between LIVERMINBBOXY and LIVERMINBBOXZ
- LIVERMINBBOX_XY_RATIO: Ratio between LIVERMINBBOXX and LIVERMINBBOXY
- LIVERBBOX_ZX_RATIO: Ratio between LIVERBBOX_ZLENGTH and LIVERBBOX_XLENGTH

- LIVERBBOX_YZ_RATIO: Ratio between LIVERBBOX_YLENGTH and LIVERBBOX_ZLENGTH
- LIVERBBOX_XY_RATIO: Ratio between LIVERBBOX_XLENGTH and LIVERBBOX_YLENGTH
- LIVERCIRCUMELLIPSE_ZX_RATIO: Ratio between LIVERCIRCUMELLIPSE_ZRADIUS and LIVERCIRCUMELLIPSE_XRADIUS
- LIVERCIRCUMELLIPSE_YZ_RATIO: Ratio between LIVERCIRCUMELLIPSE_YRADIUS and LIVERCIRCUMELLIPSE_ZRADIUS
- LIVERCIRCUMELLIPSE_XY_RATIO: Ratio between LIVERCIRCUMELLIPSE_ZRADIUS and LIVERCIRCUMELLIPSE_YRADIUS
- LIVERENTROPY: Entropy of the entire liver volume

NOTE. All local measures are calculated by using axial slices that are within ± 5 mm of the largest axial slice inside the liver volume. These are not measures derived from one single slice.

- LIVERHANNUENTROPY: Using “entropy” function of MATLAB on the local slices. This does not measure entropy of the liver; rather, it measures the relative shrinkage of the liver relative to the bounding box.
- LIVERLOCALFILLINRATIO: This measures similar feature to that of LIVERHANNUENTROPY but is more defined. It is the ratio between the number of ON and OFF pixels within the liver local slices.
- LIVERLOCALMEANAREA: Mean area of local axial slices in MM²
- LIVERLOCALPERIM: Perimeter of same local axial slices in MM
- LIVERLOCALMEANECCENTRICITY: Eccentricity of local axial slices
- LIVERLOCALMEANHU: Average Hounsfield units of local axial slices
- LIVERLOCALMEANPERIM: Mean perimeter of local axial liver slices in MM
- LIVERLOCALENTROPY: Entropy of local liver slices
- LIVERLOCALMEANMAJORAXIS: Mean major axes length of local axial liver slices in MM
- LIVERLOCALMEANMINORAXIS: Mean minor axes length of local axial liver slices in MM
- LIVERLOCALORIENTATION: Mean orientation between local axial liver slices
- LIVERLOCALMEANAXIS_RATIO: Mean ratio between major and minor axes of local axial liver slices

- SPLEENMEANHU: Mean Hounsfield unit intensity within the spleen volume
- SPLEENVOL_MM3: Total spleen volume in MM3
- SPLEENLOCALAREA: Area of largest axial slice
- SPLEENLOCALPERIM: Perimeter of the same largest axial slice
- SPLEENLOCALECCENTRICITY: Eccentricity of the same largest axial slice
- SPLEENAREA_MM2: Total surface area of spleen volume in MM2
- SPLEENINSPHERERADIUS: Radius of a best-fit sphere inscribed within the spleen
- SPLEENBBOXLENGTHMM: X length of spleen bounding box (not reoriented)
- SPLEENBBOXYLENGTHMM: Y length of spleen bounding box (not reoriented)
- SPLEENBBOXZLENGTHMM: Z length of spleen bounding box (not reoriented)
- SPLEENMINBBOX: X length of a best-fit bounding box of the spleen (reoriented)
- SPLEENMINBBOX: X length of a best-fit bounding box of the spleen (reoriented)
- SPLEENMINBBOX: Y length of a best-fit bounding box of the spleen (reoriented)
- SPLEENMINBBOX: Z length of a best-fit bounding box of the spleen (reoriented)
- SPLEENMINBBOXVOLUME_MM3: Bounding box volume of the best-fit bounding box
- SPLEENMINBBOXAREA_MM2: Bounding box surface area of the best-fit bounding box
- SPLEENMINBBOXEDGELENGTHMM: Bounding box perimeter of the best-fit bounding box
- SPLEENVOLUME_MINBBOXVOL_RATIO: Ratio of the min BBox volume and spleen volume (reoriented)
- SPLEENVOLUME_BBOXVOLUME_RATIO: Ratio of the regular BBox volume and spleen volume

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Figure 1.

(A) Example of identification of spinal vertebral levels that serve as anatomic reference system for each patient. (B) Example of fascial envelope (*yellow line*) and skin outline (*red line*) that are generated for each patient. (C) Example of the paraspinus muscles (*outlined in yellow*) defined automatically after delineation of paraspinus lateral seams at specified vertebra points that is processed in each patient. (D) Example of MATLAB based 3-D image viewer graphical user interface (GUI) generated for each segmented liver.

Figure 2.

(A) Example of bounding box of segmented liver stored in database with X, Y, and Z dimensions. (B) Example of minimal bounding box of segmented liver where the box is oriented to achieve the smallest possible bounding box and the associated X, Y, and Z dimensions. (C) Example of slice of liver that contains bifurcation of main portal vein (*) represents measured X axis distance between lateral-most liver edge and portal vein bifurcation point (LATERAL2PORTBIFURPT_XLENMM). # represents X axis distance between portal vein bifurcation to caudate lobe (PORTBIFURPT2CAUDATE_XLENMM). (D) Example of L3 relative body size measurements. Yellow line delineates fascial area (FASCIAAREA.L3). Measured area between red line (skin outline) and yellow line

delineates subcutaneous fat area (SUBCUTFATAREA.L3). ** represents measured distance from anterior surface of vertebral body to anterior midline fascia (VB2FASCIA).

Figure 3.
Receiver operating characteristic curves for final models with University of Michigan cohort.

Table 1.

Characteristics of the University of Michigan Cohort

Variable	Cirrhosis patients (n = 100), mean $\pm$ SD, median (IQR), or N(%)	Non-cirrhosis patients (n = 257), mean $\pm$ SD, median (IQR), or N (%)	P value
Male/female	52 (52.5)/47 (47.5)	141 (54.7)/117 (45.3)	NS
Age (y)	52.1 $\pm$ 12.7	48.6 $\pm$ 13.2	.022
Diagnosis			<.01
Hepatitis C virus	28 (27.3)	98 (38.1) Ishak 0,1,2,3,4, and 5 (n = 26,14,23,19,9, and 7)	
NAFLD	33 (33.3)	57 (22.2) Fatty liver, nonalcoholic steatohepatitis (n = 15,42)	
Other	39 (39.4)	102 (39.7)	
Liver transplant, Y/N	5 (5.1)/94 (94.9)	67 (26.0)/191 (74.0)	<.01
Platelet (mg/dL)	155.9 $\pm$ 101.4	22.8 $\pm$ 118.1	<.01
AST (mg/dL)	51 (38–117.5)	43 (27–91)	<.01
ALT (mg/dL)	43 (29–106)	52 (29–111)	NS
International normalized ratio (mg/dL)	1.26 $\pm$ 0.37	1.10 $\pm$ 0.27	NS
MELD	10.6 (7.5–15.3)	7.5 (6.4–11.5)	<.01
APRI (μ mol/L)	1.60 (0.84–2.75)	0.70 (0.36–1.66)	<.01
Lok Score	1.53 $\pm$ 2.73	−0.45 $\pm$ 2.18	<.01
FIB ₄	3.91 (2.39–5.55)	1.56 (0.89–3.06)	<.01

SD, standard deviation.

Table 2.

Performance of Different Predictive Models

	Training, AUROC (CI)	Internal test, AUROC(CI)	External test, AUROC (CI)
Liver and Spleen	0.85 (0.79–0.92)	0.94 (0.88–1.0)	0.92 (0.78–1.0)
All Morphomics	0.91 (0.84–0.97)	0.94 (0.87–1.0)	0.97 (0.90–1.0)
All Morphomics and Laboratory Data	0.91 (0.85–0.98)	0.95 (0.89–1.0)	0.90 (0.77–1.0)
All Morphomics Simplified	0.91 (0.85–0.96)	0.89 (0.77–1.0)	0.83 (0.58–1.0)
All Morphomics Simplified and Labs	0.88 (0.80–0.95)	0.96 (0.91–1.0)	0.92 (0.78–1.0)