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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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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.**

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 Factor; Noninvasive Markers; Advanced Technology; Fibrosis 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

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.

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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.[4–7]

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 (VAAAHS).

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 VAAAHS. 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 VAAAHS. All patients who had a liver biopsy at the VAAAHS 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.[2,8–10] 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 1*A*). 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 1*B*). The dorsal muscle groups were also defined automatically after the user delineated the paraspinus lateral seams at specified vertebra points (Figure 1*C*). 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 1*D*). For more technical information regarding the MATLAB algorithms, see Supplementary Methods. Processing of the scans was performed by trained