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Ultrasound-based tissue characterization and classification of fatty liver disease: A screening and diagnostic paradigm

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ABSTRACT

Fatty Liver Disease (FLD) is a progressively prevalent disease that is present in about 15% of the world population. Normally benign and reversible if detected at an early stage, FLD, if left undetected and untreated, can progress to an irreversible advanced liver disease, such as fibrosis, cirrhosis, liver cancer and liver failure, which can cause death. Ultrasound (US) is the most widely used modality to detect FLD. However, the accuracy of US-based diagnosis depends on both the training and expertise of the radiologist. US-based Computer Aided Diagnosis (CAD) techniques for FLD detection can improve accuracy, speed and objectiveness of the diagnosis, and thereby, reduce operator dependability. In this paper, we first review the advantages and limitations of different diagnostic methods which are currently available to detect FLD. We then review the state-of-the-art US-based CAD techniques that utilize a range of image texture based features like entropy, Local Binary Pattern (LBP), Haralick textures and run length matrix in several automated decision making algorithms. These classification algorithms are trained using the features extracted from the patient data in order for them to learn the relationship between the features and the end-result (FLD present or absent). Subsequently, features from a new patient are input to these trained classifiers to determine if he/she has FLD. Due to the use of such automated systems, the inter-observer variability and the subjectivity of associated with reading images by radiologists are eliminated, resulting in a more accurate and quick diagnosis for the patient and time and cost savings for both the patient and the hospital.

1. Introduction

Fatty Liver (Steatosis) or Fatty Liver Disease (FLD) indicates accumulation of triglycerides (fat) in the liver. Fatty liver can occur with or without the intake of alcohol. In 1980, Ludwig et al. [76] named it as Non-Alcoholic Fatty Liver Disease (NAFLD) when the fatty liver condition is independent of alcohol intake. FLD has been associated to metabolic syndrome [127], and hence it leads to several diffuse and prevalent pathologies, such as diabetes mellitus, insulin resistance, hypertension, and dyslipidemia. The accumulation of fat in the liver may eventually lead to inflammation, condition called as alcoholic or non-alcoholic steatohepatisis (ASH or NASH) and finally to cirrhosis (which describes large scale liver degeneration associated with an increased risk of hepatocellular carcinoma [95,116,19]. Studies revealed that the prevalence of

Abbreviations: ALT, Alanine Aminotransferase; AHP, Analytic Hierarchy Process; ASM, Angular Second Moment; ANN, Artificial Neural Network; CBR, Case-Based Reasoning; CART, Classification And Regression Tree; CWT, Continuous Wavelet Transforms; CAD, Computer-Aided Diagnosis; CT, Computed Tomography; DT, Decision Trees; DWT, Discrete Wavelet Transform; FFS, Far-Field Slope; FLD, Fatty Liver Disease; FDTA, Fractal Dimension Texture Analysis; FSC, Fuzzy Sugeno Classifier; GLCM, Gray Level Co-occurrence Matrix; GLDS, Gray Level Difference Statistics; RUNL, Gray Level Run Length Statistics; HOS, Higher Order Spectra; k-NN, k-Nearest Neighbor Classifier; LBP, Local Binary Pattern; MRI, Magnetic Resonance Imaging; MGL, Mean Gray Level; NAFLD, Non-Alcoholic Fatty Liver Disease; RBF, Radial Basis Function; SGLDM, Spatial Gray Level Dependence Matrices; SVM, Support Vector Machine; US, Ultrasound; WPD, Wavelet Packet Decomposition.

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FLD depends on sex [99], ethnicity [37], and age [52]. Overall, FLD affects about 15% of the world population [37,98]), and it is the most common reason for elevated liver enzymes and chronic liver disease in developed countries [18]. Early diagnosis of FLD is of paramount importance to prevent its degeneration into irreversible liver diseases, such as liver cancer [117] and acute liver failure [146]. FLD is also a major risk factor for heart attacks and stroke [138,139]. Furthermore, advanced liver diseases result in higher health care utilization, which implies higher cost for the health care provider [14].

Even though detection of FLD is easy, the differential diagnosis of FLD is difficult [149]. In fact, FLD might be linked to different factors, such as infections, inflammations, and drug or toxin-related injuries. Hepatic steatosis is usually categorized as macrovesicular or microvesicular [149]. Macrovesicular steatosis is a common occurrence in ambulatory patients, and microvesicular steatosis is associated with severe mitochondrial injury and acute hepatic dysfunction [149]. Therefore, liver biopsy is the preferred diagnostic technique for FLD detection [100]. However, biopsy is invasive, and it causes anxiety and discomfort to patients due to pain and the possibility of bleeding/hemorrhage [80]. These complications occur in at least 1.3% of all cases and the mortality ranges from 0.1% to 0.5% [17]. Given the relatively high prevalence of FLD in the general population, minimal invasive procedures have been developed for FLD diagnosis and the assessment of its degree of severity. Among all noninvasive techniques, Ultrasound (US) is the most common and widely used imaging modality for FLD diagnosis, because it is (a) inexpensive, (b) emits no harmful radiation, (c) is widely available and (d) has high sensitivity. A major downside of this imaging modality is the operator dependability [135]. Computer Aided Diagnosis (CAD) systems have been and are being developed as adjunct techniques to reduce operator dependability and to get reproducible results [30,39,113,125,49,144]. Therefore, developing CAD systems that detect early stage FLD is of utmost importance to: (a) save patients from unwanted anxiety, (b) increase the chance of recovery and (c) reduce the cost associated with providing treatments for advanced liver diseases [7].

In this paper, we first review the advantages and limitations of current modalities that are used for FLD detection (Section 2). Subsequently, we discuss the structure of an US-based CAD system and briefly describe the features that are extracted from the US images and the commonly used classification algorithms (Section 3). We then review the methodology and evaluation results of several CAD systems proposed in the literature (Section 4). In these techniques, first informative features are extracted from the US images. The features are used as input to train automated decision making systems. Coupling feature extraction with automated classification provides a way to evaluate the features in a practical setting, i.e. it is a way to find out how useful these features are for a working radiologist. After careful analysis of the literature, we found that the US-based CAD techniques for FLD can improve accuracy, speed and objectiveness of the diagnosis, and thereby, reduce operator dependability. We conclude the paper in Section 5.

2. Literature review

2.1. Liver

The liver is the heaviest and the largest glandular organ in the human body and it is absolutely crucial to life [12]. The liver performs vital functions: synthesis of proteins, fats and fatty acids, metabolism and storage of carbohydrates, and bile production and excretion. It maintains both volume and quality of blood by filtering potentially harmful biochemical products from the blood. One of these harmful products is bilirubin, which forms during the breakdown of old blood cells [134]. Another harmful product is ammonia, which forms during the breakdown of proteins [75]. The human body produces both bilirubin and ammonia constantly. The liver is also responsible for filtering harmful substances from external sources, such as drugs, alcohol and environmental toxins. Thus, any disturbance to these detoxifying functions leads to poor health.

2.2. Liver disease

Liver disease can be due to infection, injury, drug exposure, toxin presence, autoimmune processes, or genetic defects that result in the accumulation of iron or copper. Liver disease results in inflammation, scarring, fibrosis, obstructions, clotting abnormalities, and liver failure [132]. A common example of liver disease, which is gaining increasing recognition worldwide, is FLD [78].

2.3. Fatty Liver Disease (FLD)

FLD is a spectrum of conditions, which are predominantly characterized by hepatic steatosis, the accumulation of fat-containing vacuoles within hepatocytes [28]. This accumulation of triglyceride fats happens through a process of steatosis, whereby there is an abnormal retention of lipids within cells [117,94]. Chronic alcohol abuse is one of the main causes of FLD. About 90% of individuals who drink more than 60 g of alcohol a day develop FLD [25]. Other causes of FLD include insulin resistance and all forms of the metabolic syndrome, such as obesity, Type 2 diabetes, arterial hypertension, and hyperlipidemia [1]. Based on the causes, there are two FLD types: Alcoholic Steatosis and Non-Alcoholic Fatty Liver Disease (NAFLD). The term FLD can indicate asymptotic steatosis, with elevated or normal aminotransferases to steatohepatitis, cirrhosis with liver function complications, and even hepatocellular carcinoma [11]. For milder forms of FLD, the accumulation of excess fats in the liver is usually benign and fully reversible [101]. Left untreated, the disease is likely to progress further to irreversible advanced forms.

2.4. Diagnosis of Fatty Liver Disease (FLD)

Early and accurate diagnosis of FLD is of significant clinical importance, because disease incurred damage can often be reduced or reversed with proper treatment. It also helps health care providers by reducing the number of subjects with advanced liver diseases. Hence, the overall healthcare cost comes down. The diagnosis of FLD requires evidence of fatty liver tissues. Currently, a range of methods is used to obtain this information. These methods are classified as invasive [101] and noninvasive [95,20,41,86,128,104]. We briefly describe these diagnosis methods in the following paragraphs, and present a summary of these methods along with their advantages and limitations in Table 1.

2.4.1. Blood tests

Liver function blood tests are one of the most commonly performed analysis steps during routine medical checkups. The blood drawn from a patient undergoes centrifuge treatment and the resultant blood serum is then subjected to a battery of tests. These tests can assess basic liver functions, liver injury and liver diseases, like FLD. For example, the presence of certain enzymes (proteins) in the blood indicates liver damage or liver disease [114]. Usually, these enzymes are present within the liver cells. In the event of liver damage, due to disease or injury, these enzymes spill into the blood stream where they can be detected by routine blood tests. Among these blood tests, aminotransferase is the most sensitive detector of FLD [63], and the related tests are called Aspartate Aminotransferase (AST) test and Alanine Aminotransferase (ALT)