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Computer-Aided Diagnosis of liver lesions using CT images: A systematic review

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Computer-Aided Diagnosis of liver lesions using CT images: A systematic review

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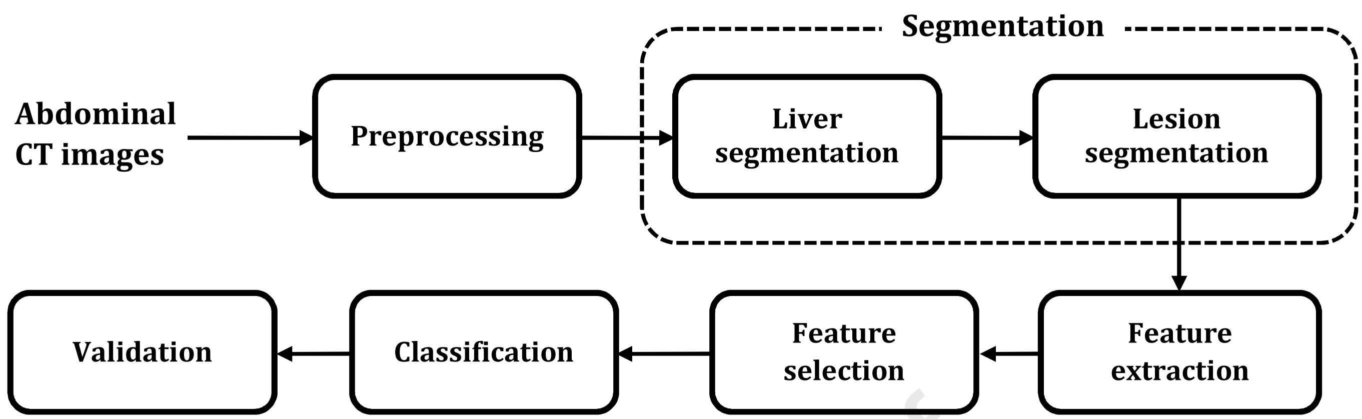
ABSTRACT

Background: Medical image processing has a strong footprint in radio diagnosis for the detection of diseases from the images. Several computer-aided systems were researched in the recent past to assist the radiologist in diagnosing liver diseases and reducing the interpretation time. The aim of this paper is to provide an overview of the state-of-the-art techniques in computer-assisted diagnosis systems to predict the benign and malignant lesions using computed tomography images.

Methods: The research articles published between 1998 and 2020 obtained from various standard databases were considered for preparing the review. The research papers include both conventional as well as deep learning-based systems for liver lesion diagnosis. The paper initially discusses the various hepatic lesions that are identifiable on computed tomography images, then the computer-aided diagnosis systems and their workflow. The conventional and deep learning-based systems are presented in stages wherein the various methods used for preprocessing, liver and lesion segmentation, radiological feature extraction and classification are discussed.

Conclusion: The review suggests the scope for future work as efficient and effective segmentation methods that work well with diverse images have not been developed.

Furthermore, unsupervised and semi-supervised deep learning models were not investigated for liver disease diagnosis in the reviewed papers. Other areas to be explored include image fusion and inclusion of essential clinical features along with the radiological features for better classification accuracy.


Segmentation
Abdominal CT images
Preprocessing
Liver segmentation
Lesion segmentation
Feature extraction
Feature selection
Classification
Validation

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Keywords

Computer-aided detection/diagnosis, liver diseases, Hemangioma, Hepatocellular carcinoma, liver/lesion segmentation, feature extraction, classification, deep learning

1. INTRODUCTION

Liver diseases account for about 2 million deaths every year globally [1]**.** According to World Health Organization, liver cancer was the sixth most commonly diagnosed cancer and fourth leading cause of cancer death in 2018 [2]. The liver is one of the most common organs to develop metastases [3].

Computed Tomography (CT) is the most widely used modality for diagnosing liver diseases [4–6]**.** To assist a radiologist in interpreting the CT images, several computer-based systems like Computer Aided Diagnosis (CAD_x), Computer-Aided Detection (CAD_e) and Content-Based Medical Image Retrieval (CBMIR) are proposed by researchers. The CAD_e systems only detect and mark the suspicious areas like lesions in an image, whereas the CAD_x systems not only mark suspicious areas but also report the likelihood that the detected lesion is of a specific type (for instance, malignant/benign) [7,8]. The CAD_x and CAD_e systems shall hereafter be referred commonly as Computer-Aided detection and Diagnosis (CAD) systems. The CAD systems reduce the workload of the radiologists by providing a fast and precise diagnosis. Whereas the CBMIR systems offer decision support to radiologists by retrieving similar images from the medical database based on extracted radiological features [9]. The primary focus of this review is on the CAD systems; however, the feature extraction techniques employed in some of the CBMIR systems are also discussed.

The CAD system development involves the integration of multiple disciplines like image processing, pattern recognition, artificial intelligence and medical imaging. The hepatic CAD pipeline consists of various stages namely preprocessing, segmentation, feature extraction and selection; and classification. It takes abdominal CT images as input and processes them to detect/diagnose the liver lesion. In this review, the CAD systems are grouped into two categories: first conventional and second deep learning based. The two systems mainly differ with respect to the feature extraction stage. In the conventional CAD systems, the discriminatory features that characterize the liver/liver lesions are chosen by the CAD system developer. On the other hand, in the Deep Learning based CAD (DL-CAD) systems the pertinent features are automatically extracted by the DL algorithm. For each of the two CAD systems, the different methods employed in the various stages, are reported along with their merits and demerits. This approach of analysis is adopted as it helps in viewing the CAD systems from a broader perspective. Besides, the paper also includes some state-of-the-art liver lesion segmentation methods as they can be incorporated in the CAD systems.

In the reviewed CAD systems various Focal Liver Lesions (FLL) are categorized. They include Liver Cancers (LC) like Hepatocellular Carcinoma (HCC), Cholangiocarcinoma (CC) and Metastasis (MET) and benign liver lesions like

Hemangioma (HEM), Focal Nodular Hyperplasia (FNH), Hepatic Adenoma (HA), cysts and Abscess (ABS). A pictorial description of this categorization is shown in Fig. 1.

Fig. 1. A pictorial description of the FLLs considered in the reviewed papers.

A small minority of the reviewed papers have also considered Cirrhosis (CIRR). Since patients with CIRR are at a high risk of developing HCC [10]. The CT images indicating the discussed liver anomalies are shown in Fig. 2, the terms portal venous and arterial mentioned here are discussed in the next section. Hereafter, the terms FLL, hepatic/liver lesion and lesion will be used interchangeably.

Fig. 2. Abdominal CT images indicating the liver anomalies along with the phase [11] (arrows were not shown in original images. For sake of explanation we have included them).

In the majority of the literature, the researchers have attempted to identify the types of FLL. Others have either tried to differentiate between Benign (B) and Malignant (M) lesions in general without considering the subtypes or classified the liver as Normal (N) or Abnormal (ABN). A broader insight into the various categories considered for classification in the reviewed CAD systems is provided in Table 1.

Table 1. Categories considered for classification in the reviewed CAD systems.

The remaining part of the paper is structured into the following sections: Section 2 briefly discusses the visualization of the common liver lesions in various CT phases. Section 3 describes the general architecture of the reviewed CAD systems. Further, the various methods adopted in the conventional CAD systems for image preprocessing, segmentation; feature extraction and selection; classification and the various evaluation measures are also elaborated. In Section 4, the DL based hepatic lesion segmentation techniques and CAD systems are reviewed. Section 5 discusses the limitations and highlights the areas for future research and Section 6 concludes the review.

2. CT phases and liver lesions

In clinical practice, liver abnormalities, especially liver lesions, are diagnosed by observing and comparing their enhancement patterns in Non-Enhanced CT (NECT) and various Contrast-Enhanced CT (CECT) images. The former refers to the CT images acquired before the injection of an iodinated intravenous contrast agent, whereas the latter comprises two phases, namely Arterial (ART) and Portal Venous (PV), acquired typically 20-30s and 60-80s post-injection, respectively [53]. Also, there are other phases like Delayed (DLY) and Equilibrium (EQ) that are used for diagnosis by radiologists. In NECT images, the lesions are less conspicuous due to the inherent low contrast between most lesion tissues and surrounding liver parenchyma making it essential to acquire CECT images [54]. The visualization of the common FLLs in different CT phases (on axial slices) is shown in Fig. 3 and the typical radiographic features used for differentiating these lesions are summarized in Table 2.

Fig. 3. Visualization of common liver lesions (on axial CT) in NECT, ART, PV and DLY phases (adapted from [55]).

Table 2. Typical radiographic features of common liver lesions from other studies.

Some of the papers reviewed in this article have considered only NECT images, while the others have worked with some or all of the CECT phases. The details regarding the same are reported in Table 3. However, some researchers have not provided information about the type of CT images used in their work.

Table 3. Summary of the CT phases employed in the reviewed papers.

Although the CECT images contain more details than NECT images, a few authors have preferred the latter. The iodinated contrast agent causes renal toxicity and allergic reactions in some patients and are unsuitable for patients with diabetes and kidney disorders [14,15,42]. However, such systems have a higher probability of missing lesions that do not show up in these images [15]. In [42], an innovative image enhancement method based on fuzzy histogram equalization, contourlet domain and decorrelation stretching was proposed to facilitate the accurate diagnosis of lesions.

3. CAD workflow

A conventional CAD system typically comprises five stages, namely (1) Preprocessing (2) Segmentation (3) Feature Extraction (4) Feature Selection and (5) Classification, as shown in Fig. 4. These stages are implemented using various image processing, pattern recognition and Machine Learning (ML) techniques.

Fig. 4. Block diagram of a conventional CAD system comprising of preprocessing, liver and lesion segmentation, feature extraction, feature selection and classification stages.

The conventional CAD systems reviewed in this article, have adopted different versions of the five-stage pipeline mentioned above. The pipeline followed in some of the CAD systems [10,12,22,24,25,29,33,39,46] along with the common techniques employed is summarized pictorially in Fig. 5. A brief description of the same emphasizing the workflow is given below.

The CAD systems use either CECT (single/multiple phase(s)) or NECT images of the abdomen as discussed in Section 2. Although preprocessing is an important stage, some authors skip this stage and perform segmentation directly on the input images; and report good results. In most of the work, segmentation was performed in two stages (liver followed by lesion segmentation) as will be detailed in Section 3.2; nevertheless, there are exceptions. Some authors prefer to perform segmentation only once either to delineate liver or lesion. Subsequently, relevant features are extracted from the segmented image. The next stage, namely feature selection is opted by a few authors, others directly proceed with classification after feature extraction. Each of these stages are discussed in detail in the subsequent subsections.

More recently, the advent of DL technology has brought about major changes in CAD system development. These changes mainly pertain to the feature extraction stage. In the reviewed DL-CAD systems, one or more of the stages namely, segmentation, feature extraction and classification were implemented through DL algorithms. The DL-CAD systems are discussed in Section 4.2, while the conventional CAD systems are elaborated in the following subsections.

Fig. 5. A pictorial overview showing the workflow adopted and prominent techniques used in the reviewed conventional CAD systems.

3.1 Preprocessing

The main purpose of preprocessing is to augment the quality of the acquired CT images to achieve accurate outcomes in subsequent stages. Image noise (mottle), contrast and spatial resolution are the principal factors that define image quality. The main reasons for image noise are beam hardening, streak artifacts and motion artifacts [64]. In the reviewed literature, the major focus was on noise alleviation and contrast enhancement. The liver mostly shares weak boundaries with adjacent abdominal structures and the lesions usually have vague edges. Hence it is imperative that the filters employed for noise suppression are edge-preserving as well. Since median filter is a simple filter that satisfies this requirement it was used in [16,29,30,65,66] for noise mitigation. In [12], a detail preserving median-type filter elaborated in [67] and an anisotropic diffusion filter were used. The various denoising methods suitable for CT images are discussed in [68].

Among the contrast enhancement approaches, simple histogram equalization was used in [14,15,65]. In [42], an innovative method was presented to accentuate the contrast of the NECT image in two stages using the non-sub-sampled contourlet transform domain. In the first stage, fuzzy histogram equalization was performed and in the second stage, decorrelation stretching allotted separate colors to different tissues to facilitate delineation. A computationally efficient cross-modality technique based on 2D histogram specification employing CT and magnetic resonance images was proposed in [69], while mean shift method was used in [70]. Several transform based contrast enhancement methods employing morphological top hat transform [71], wavelet transform [72] and contourlet transform [73] were investigated by researchers. Their applicability to the present context can be explored.

The authors of [46,66], eliminated the non-hepatic regions from the CT image based on prior knowledge of the anatomy to speed up segmentation. The authors of [16] relied on resizing the image for achieving the same.

3.2 Segmentation

Segmentation delineates the desired anatomical or pathological regions from the image and is a crucial stage, as imprecise segmentation can eventually lead to misdiagnosis. Semi or fully automated or completely manual segmentation approaches were adopted in the reviewed literature. In manual segmentation, the radiologist contours the lesions, but it largely varies due to inter and intra operator variability and is a time-intensive task [74]. However, a large part of the published literature has relied on manual contouring. This scenario may be attributed to the difficulties associated with hepatic lesion delineation, which include heterogeneous densities and weak boundaries [75]. Also, the intensities of the liver lesions are very close to that of other non-hepatic structures in the abdomen [22]. To handle this issue, in the rest of the literature~~,~~ segmentation was done hierarchically (first liver, then lesion) using automatic or interactive methods. It comprises a two-step strategy, wherein the liver was first delineated from the abdomen, followed by lesion segmentation from the segmented liver. Some researchers have only performed liver segmentation and skipped lesion delineation. However, liver segmentation is itself very challenging due to the closely related intensities between the liver and its adjacent organs, namely heart and stomach [74]. Furthermore, inter/intra patient variations in the liver structure, which worsens in a pathological liver, vague boundaries with adjoining structures and division of liver into two lobes in the final slices of a patient dataset also pose difficulties. Some of these issues associated with automatic liver segmentation are illustrated in Fig. 6.

Fig. 6. CT images showing difficulties associated with liver segmentation (labels were not shown in the original images. For the sake of explanation we have included them)

3.2.1 Liver segmentation techniques

Researchers have investigated various segmentation algorithms for delineating the liver. In [22,66], first, thresholding was applied to discard the pixels external to the hepatic intensity range estimated from the histogram of the CT image. Then, morphological erosion was performed to eliminate the non-hepatic tissues of similar intensity that get segmented along with the liver. Finally, the confidence-connected region growing technique was applied by taking the centroid of the largest connected region as the seed point to extract the liver automatically. Nayak *et al.* [10] proposed an interactive region growing method that accepted seed point input from the user only for the first slice and computed the same intelligently for subsequent slices. A remarkable feature of their work was the automatic detection of segmentation error and prompting the user to input seed points to rectify the same. Furthermore, their approach efficiently handled the issue of liver getting partitioned into two or more lobes. Although region growing is a simple and potent algorithm, it results in leakages when the regions to be delineated have weak boundaries. Hence they have to be preceded and succeeded by several image processing operations to get accurate results.

Some authors have explored hybrid segmentation approaches that integrate multiple techniques to get better solutions. In the work by Chen *et al.* [24], Normalized Fractional Brownian (NFB) feature bit map and region growing were employed to obtain a rough estimate of the liver. Subsequently, a deformable contour model refined this output. A few researchers have explored the usefulness of neutrosophy in segmentation as they give good results in low contrast medical images with fuzzy boundaries [76]. The input image was transformed into the neutrosophic domain in [29] and [65]**.** While the former performed Fuzzy C-Means (FCM) thresholding on the transformed image to delineate the liver, the latter applied adaptive thresholding, morphological operations and watershed algorithm to achieve the same. Ranjbarzadeh *et al.* [70]**,** used the Kirsch filter for edge detection. This was followed by the identification of the concave and convex points of the structures adjacent to the liver. Then the mean-shift algorithm was used for selectively enhancing the borders. The close concave points were subsequently linked to detach the liver from the adjacent organs and FCM clustering was applied to extract the liver contour. The high computational cost demanded by the hybrid methods needs to be reduced to render them suitable for practical applications.

In [13,30,38,46], the histogram of the input image was analyzed to find the approximate intensity range of the liver region. This was followed by thresholding to retain only those pixels that lie within the range. Morphological opening and closing operations were then performed to remove the unwanted structures attached to the liver. As indicated earlier, this approach was used in [66] as a preliminary step before the actual segmentation. Although it is a simple and computationally inexpensive method, it may not produce precise contours when there are large peripheral lesions in the liver. An attempt was made in [32] to address this issue.

FCM was used in [77], where the abdominal CT image was partitioned into three clusters, namely liver, lesion and background. In [39], marker controlled watershed algorithm was applied to extract the liver effectively. This method resolves the over-segmentation issue commonly encountered in traditional watershed segmentation. Most of the aforementioned segmentation methods were coupled with morphological operations to refine the segmentation results.

3.2.2 Lesion segmentation techniques

Most of the authors preferred to manually delineate the lesions [14,15,48,51, 78,26,28,33–35,40,42,43]. FCM with three clusters corresponding to liver, lesion and background was used in [13,16,18,22,30,38,65,70,79] and was the next most popular method. In [18], region growing was performed post FCM segmentation with seed point taken automatically from the lesion cluster to further improve the results. The work in [77] also adopted region growing in a similar way.

Chang *et al*. [12] applied semiautomatic confidence connected region growing to extract the lesion volume directly from the abdominal CT images. In [69], a computationally efficient lesion segmentation method inspired by gradient-based seeded region growing was used. In [32], the filling defects that occurred when the liver was delineated using thresholding were considered as central lesions and an alpha shape type algorithm was used to detect the peripheral lesions. However, a shortcoming of their method was that it did not segment the large border lesions well. Nevertheless, it needs to be noted that their work was the only study among the reviewed literature that addressed the issue of liver contour refinement when peripheral lesions are present.

Sun *et al.* [45] combined the Distance Regularized Level Set Evolution (DRLSE) method and region growing, while in [39], a Gaussian Mixture Model (GMM) was used. Level set methods were sparingly used for lesion delineation probably due to their high computation time. The work in [49] combined flood filling and iterative adaptive thresholding algorithms. In [61], a method was proposed that automatically detected hepatic lesions having distinct characteristics efficiently using intensity analysis and multilevel geometric features. While in [80], a generative model integrated with knowledge constraint was used, a framework that fused generative and discriminative models was developed in [81]. In [82], an object-based image analysis approach was adopted for detecting hypodense lesions. The success of any segmentation method depends on its robustness, accuracy and processing speed. However, it was observed that a vast majority of the researchers had used only one dataset and not divulged information regarding the accuracy and processing speed. Table 4 reports the prominent segmentation methods used for liver and/or lesion delineation in the reviewed literature.

Table 4. Summary of the liver and/or lesion segmentation methods used in the reviewed literature.

Some of the pros and cons of the prominent segmentation algorithms are listed in Table 5.

Table 5. Pros and cons of the prominent segmentation algorithms.

3.3 Feature extraction and selection

Feature extraction is the computation of the most relevant descriptors from the segmented image such that the intraclass variance is minimized and the interclass variation is enhanced to facilitate accurate classification [83]. Liver lesions are principally characterized by texture descriptors using statistical approaches. Gray Level Co-occurrence Matrix (GLCM), which studies the correlation between pairs of pixels with a certain spatial relationship were extensively utilized to characterize hepatic lesions. Other texture extraction techniques investigated in the reviewed literature include Laws' Texture Energy Measures (LTEM), fractal and histogram based methods, Local Binary Pattern (LBP) and Gray Level Difference Matrix (GLDM). Some authors have extracted texture features from the multiscale representations of the segmented lesions. In [46], wavelet decomposition followed by GLCM feature extraction was done. Kumar *et al.* [22] showed that Contourlet Coefficient texture features were more effective in discriminating the benign and malignant lesions than Wavelet Coefficient and gray level texture features. In [77], the difference between the features computed from the lesion and normal hepatic tissues were used to differentiate the lesions. The efficacy of Zernike and Legendre moments in representing the lesions were investigated in [28].

Since radiologists identify the liver lesions by studying the visual patterns generated in the multiple phases of CT, it is essential that the feature vector includes details from different phases. In [43,84], texture features derived from different phases were combined to characterize the lesions. Roy *et al*. [55] presented a framework in which the lesion volume is divided into three partitions to capture the central, intermediate and border characteristics of the lesion tissues in a time-efficient manner. The effective spatial and temporal features were then extracted from multiple phases. More recently, Nayak *et al.* [10] computed temporal features such as minimum signal intensity, peak signal intensity, time to peak, intensity difference between various phases and so on to assimilate the contrast enhancement pattern across multiple phases. In [45], time series features like relative signal intensity, signal enhancement ratio and so forth were computed for three phases along with histogram and GLCM features.

Mid-level features based on Bag-Of-Visual-Words, are increasingly being researched in medical applications. They are adapted from the original Bag of Words model used for text analysis and represent images by histograms of image features, also called visual words. In [48], dictionaries corresponding to lesion margin and interior were created to characterize three types of hepatic lesions. Other studies that investigated this model are [85–87].

Some authors [16,18,32,39,40,61,77] have also explored geometric and shape features. Among other techniques, multidimensional persistent homology was investigated in [78] for feature vector generation. Table 6 presents a summary of the common feature extraction methods explored in the reviewed articles.

Table 6. Summary of the commonly used feature extraction techniques.

Feature extraction is usually followed by feature selection wherein the ineffective extracted features are pruned; thereby reducing computational cost and improving classifier performance [88-90]**.** Genetic Algorithm (GA) [33–35] and Principal Component Analysis (PCA) [22,26,40,45] were prominently used for this purpose. Thomaz *et al.* [51] proposed a novel GA approach based on the Mahalanobis metric for feature selection. Other methods used were forward selection and backward elimination algorithms.

3.4 Classification and evaluation measures

Classification is the final stage of a CAD system that performs the desired categorization by using the ML concepts. Various classifiers were investigated by the researchers to categorize the liver/liver lesions. Support Vector Machine (SVM), which performs classification by computing an optimal hyperplane with a maximum margin between two categories [40], was a significant classifier in the present context. SVM with Radial Basis Function (RBF) kernel was used in [16,26,78]. In [42], a multiclass SVM based on one-versus-one method was employed to classify lesions into six categories. Other works employing SVM include [14,25,29]. Artificial Neural Networks (ANN) that mimic the biological Neural Network (NN) of the brain were also employed in many CAD systems. Probabilistic Neural Network (PNN) classifier was used in [13,46]. Chen *et al.* [24] used its modified version for lesion classification. Multilayer Perceptron Neural Network (MLPNN) was adopted in [15].

Apart from the classifiers mentioned above, an ensemble of classifiers that groups several weak learners to form a strong learner was employed in [18,34]. In [40], K-Nearest Neighbor (KNN), ANN, SVM and Random Forest (RF) classifiers were combined with the majority voting scheme for categorizing the lesions. Mougiakakou *et al.* [33] built an ensemble classifier using one MLPNN, one PNN, three distinct KNNs and a weighted voting scheme. Another approach employed was cascading two or more similar or dissimilar ML models to obtain the classifications in stages. Nayak *et al*. [10] used a Logistic Regression (LR) classifier to classify liver into normal/diseased, followed by SVM with RBF kernel for classifying diseased liver into CIRR/HCC. A cascade of three SVMs was used in [45], while a similar approach with NNs was adopted in [35].

Among the other classifiers, the Naïve Bayes (NB) classifier was investigated in [25,30], C4.5 decision tree classifier was used in [38] and Euclidean distance classifier was adopted in [28]. It was observed that SVM and ANN classifiers primarily performed binary classifications while the ensemble and cascaded classifiers were employed when lesions were to be categorized into three or more classes.

K-fold Cross-Validation (CV) (10 folds in [14,15,25,38,43], 5 folds in [45,77] and 3 folds in [39]) was the most commonly used validation and test technique. Its simpler version, leave one out method was applied in [12,18,32,48,78] and bootstrap method was used in [33]. The simple holdout approach was employed in [13,22,26,27]. The CV techniques generate a robust ML model at the cost of high computation time. On the other hand, the holdout approach performs fast processing and is preferred when the dataset is large in size. But such ML models are more likely to be sensitive to the training data.

The key metrics used for evaluating the performance of the CAD system are accuracy, sensitivity, specificity, area under the receiver operating characteristic curve, positive predictive value and negative predictive value. A summary of the prominent feature extraction and ML techniques used in some of the CAD systems, along with their sample size and performance measures is given in Table 7. In the reviewed literature on conventional CAD systems, different datasets were used, to train and test the model. The researchers have relied on datasets from private hospitals, mainly due to the unavailability of a large scale database for liver diseases. As a result a fair comparison between the different CAD systems cannot be done.

Table 7. Overview of the CAD systems in terms of sample size, feature extraction & selection techniques, classification methods and performance.

4. DL technology

In recent years, DL algorithms are increasingly being researched and applied in the medical imaging domain for lesion segmentation, characterization and classification. This shift is largely attributed to the availability of powerful graphics processing units, big data and advances in DL algorithms. Another contributing factor is the automatic selection of relevant features in the DL based systems when compared to the conventional CAD systems where domain expertise is required for selecting the handcrafted features making it a challenging task [91–93].

A large proportion of the hepatic DL-CAD systems were based on Convolutional Neural Networks (CNN). These networks typically comprise pairs of convolutional and pooling layers, followed by Fully Connected (FC) layers and, finally, a softmax layer to produce the desired classifications; however, variations are seen in the modern versions [94]. Some of the common CNN models are LeNet, AlexNet, VGGNet and Residual Neural Network (ResNet). In most of the reviewed literature, CNN and related networks were used for feature extraction and classification, whereas Fully Convolutional Networks (FCN) and their variants like UNet were adopted for liver/liver lesion segmentation. In a broader sense, FCN is a CNN with the FC layer replaced by deconvolutional (or transposed convolutional) layer to perform pixel wise classification. The DL based liver lesion segmentation methods and hepatic CAD systems are discussed in the following subsections.

4.1 DL based segmentation

UNet, a symmetrical encoder-decoder network with skip connections, developed for biomedical image segmentation was used by many researchers. In [95], two UNet based models were cascaded to segment liver lesions from the abdominal CT images hierarchically. Then, a 3D Conditional Random Field was used for refining the lesions. Li *et al*. [96], formulated a hybrid framework by combining 2D and 3D UNets to efficiently segment liver lesions from CT volumes. The 2D densely connected UNet computed intra-slice features and its 3D counterpart merged the volumetric features hierarchically using the auto-context approach. These features were later jointly optimized using hybrid feature fusion layer. Their approach addressed the issue that 2D networks ignore the third dimension and that the 3D networks are computationally expensive. However, the efficacy of the algorithm in segmenting small liver lesions needs to be ascertained.

Cheon *et al.* [97] proposed a DL approach based on UNet model that explored the usefulness of the CT attenuation value in differentiating lesions from normal tissues. The weighted dice loss function was used for training the model, which exhibited improved performance compared to conventional UNet.

In [98], a DL model inspired by ResNet and UNet performed segmentation in two stages. While the first stage coarsely delineated the liver region, the second stage performed both liver and lesion segmentation. The former stage extracted the multiscale features from the input image while the latter worked on the edge information. Their framework performed better than other existing methods especially when liver and liver lesions had ambiguous boundaries. However, the framework was less effective in delineating small lesions and may require the incorporation of more spatial and contextual information to tackle the same.

Bai *et al*. [99], proposed a hybrid framework that integrated DL and conventional methods to segment lesions effectively. A 3D UNet was initially used to extract the liver region from the CT volume. The segmented liver image was then segregated into lesion candidates using a multi-scale superpixel segmentation method. Then, a 3D Fractal Residual network that combined fractal and residual structures identified the lesions from these lesion candidates. Finally, an active contour model was used for refining the lesion boundary. Although their complex algorithm outperformed a few existing methods, it had some limitations, for instance, the precise lesion contours could not be obtained. Besides, the algorithm was ineffective in discriminating between multiple adjacent lesions.

In [100], a modified SegNet with a binary classification layer was used for lesion segmentation. A pitfall of their method was false positive detection. SegNet was originally proposed for scene understanding but is now increasingly being adopted for medical image segmentation applications. This trend may be due to their efficiency in terms of memory requirement, training time and accuracy.

Nanda *et al*. [101] used a SegNet model for liver delineation, followed by a genetically optimized ANN network fed by LTEM features for initial lesion detection. The output of ANN was input to UNet for final lesion segmentation. They showed that UNet gives better results with limited dataset when compared to SegNet.

In [102], two deep Encoder-Decoder CNNs (EDCNN) having network architecture similar to SegNet were employed for segmentation. The input images preprocessed through Hounsfield windowing and histogram equalization were applied to the first EDCNN for segmenting the liver. The lesion was delineated from the segmented liver by the second EDCNN. Nevertheless, the lesion segmentation accuracy achieved by the algorithm was not very high.

Patch-based CNN was used in [103] for liver lesion delineation. But, the conventional CNNs are less frequently used for segmentation due to their high computational complexity. Sun *et al*. [104] performed the automatic delineation of hepatic lesions from triphasic CECT images using multi-channel FCN. The network was trained using the different CT phases and the extracted features were finally fused in the high-level layers.

It was observed that although most of the DL based segmentation techniques delineated the larger lesions well, they were not as effective for the small lesions. The downsampling and upsampling in the DL models may be causing loss of important details from the small lesion images, which already have less voxels, making it difficult to accurately classify the voxels corresponding to these lesions. Unlike, the conventional segmentation methods, the DL methods require training the model, have higher computational complexity and are mostly automatic.

4.2 DL based hepatic CAD systems

The reviewed hepatic DL-CAD systems, derived their workflow from the general pipeline: preprocessing, liver and liver lesion segmentation, feature extraction and classification. It was noted that in some of the papers both conventional as well as DL methods were used to implement the pipeline. Others, mostly relied on DL methods. The following subsections discuss the methods employed at the various stages of the DL-CAD system.

4.2.1 Preprocessing

The preprocessing operations in DL-CAD systems were largely limited to resizing the input images to a dimension suitable for the respective DL model. For example, Yasaka *et al.* [63], resized the input images from 500X500 to 70X70 pixels to decrease the memory requirement and execution time. But, it usually results in loss of crucial details which can adversely impact the accuracy of the DL-CAD system. To address this issue, in [19,20] Discrete Wavelet Transform (DWT), Singular Value Decomposition (SVD) and perceptual hash function were applied to downsample the input CT images while retaining their salient features. They achieved high accuracy with 32X32 size images downsampled through this approach.

The typical image processing based preprocessing operations applied in conventional CAD systems were rarely used here, barring a few exceptions. For instance, in [17], median filtering and histogram equalization were performed on the input CT images. Multi-temporal fusion of ART and PV phase CT images and decorrelation stretching were adopted in [105]. These operations improved the segmentation and classification accuracies of the DL-CAD system.

4.2.2 Segmentation

The strategies adopted for liver lesion segmentation in DL-CAD are mostly reminiscent of those used by their conventional counterparts. In [17], liver lesion was segmented hierarchically using SegNet and UNet. Besides, to reduce the computational complexity of the framework, the hyperparameters of the DL models were optimized through Artificial Bee Colony (ABC) algorithm. In [50], a variant of FCN-8s was adopted for semantic segmentation of liver and lesion. They reported that their network achieved good segmentation accuracy and required lesser training time compared to UNet. But, a pitfall was that it produced noise spots in some cases. FCN was also used for lesion detection/segmentation in [52, 47].

Some researchers, as mentioned earlier, relied on conventional segmentation techniques. In [105], region growing and region merging were used for lesion segmentation. Liang *et al.* [37], applied an interactive random walk-based segmentation technique to segment FLLs. In [106], only the liver was delineated and iterative probabilistic atlas model was used for the purpose. When conventional methods are used, the researcher needs to put in a lot of effort to come up with an effective segmentation algorithm. In that sense, the incorporation of DL algorithm reduces human effort but at the cost of high computational complexity.

The liver lesions were manually segmented in [31,36]. Unlike conventional CAD systems, some DL-CAD systems [19–21] refrained from performing any type of segmentation. In such DL-CAD systems, the preprocessed input abdominal CT images were directly given to the feature extraction stage. This greatly reduces the computational complexity of the DL-CAD system. Besides, such systems have demonstrated excellent classification accuracies.

4.2.3 Feature extraction and classification

The different CNN models were investigated by the researchers for feature extraction and classification. In [17], LeNet-5 model optimized by the ABC algorithm was used for liver cancer diagnosis. The optimization technique aided in reducing the computation time and enhancing the performance of the model. In [50], a modified version of VGG-11 was used for characterizing and classifying HCC into three types namely, diffuse, nodular and massive. The CNN classifier was also compared with ANN and SVM classifiers trained with gray level features and it was found that on an average the CNN classifier outperformed the conventional classifiers. In [63], a CNN comprising six convolutional layers, three max pooling layers and three FC layers was used for characterizing and classifying FLLs. The authors reported low sensitivity for certain lesions.

In [36], the effectiveness of ResNet and AlexNet CNN models in differentiating four FLLs (Cyst, FNH, HCC and HEM) was compared and it was found that ResNet showed better performance. Other CAD systems that used CNN and its derivatives for feature extraction and classification were [31,47].

The DL-CAD systems discussed so far extracted only the high level features through CNN. These features, however, cannot capture the local and global details from the image comprehensively. Besides, they cannot represent the temporal enhancement patterns. Hence, Liang *et al.* [37], proposed a framework to address these issues. ResNet with global and local pathways (ResGL Net) fed with two inputs namely, Region Of Interest (ROI) and patches corresponding to healthy tissues and FLLs was used to extract the local and global features from each phase. In addition, a Bi-Directional Long Short-Term Memory (BD-LSTM) was used to capture the enhancement patterns across the multiphase CT images. Since LSTM is a Recurrent NN which deals with sequential data efficiently, it was explored by other researchers as well.

In [21], a three stage framework was proposed in which, first, an AlexNet based CNN was used for extracting the feature vector from the input CT image. Then, the dimension of the feature vector was reduced and relevant features preserved using ~~a~~ one-dimensional DWT. The LSTM classifier then categorized the lesions into benign and malignant, based on these features. However, the CAD system cannot identify the specific type of the lesion.

As mentioned earlier, in some of the DL-CAD systems, conventional ML algorithms were used for classification. For example, in [19] extreme learning machine classifier trained with CNN features was employed. Likewise, SVM was used in [37, 41] and ANN in [20] for lesion categorization. These DL-CAD systems based on ML classifiers trained with CNN features, have shown promising results in lesion classification.

4.2.4 Other issues

The main challenge with the DL technology is the requirement of a huge amount of annotated data. A large dataset can help alleviate overfitting and improve the generalizability of the DL model. In this regard, various strategies were adopted by the researchers. Data augmentation approaches which artificially increase the number of images, was one of the most prominent strategies. Data augmentation by applying transformations like flip, rotation, scale, translation and so on, on the existing data was the most commonly used approach. It was adopted in [19,20,47,52,63]. Although this approach can increase the size of the dataset, it cannot generate images of diverse lesions. The synthesized lesion images will only contain patterns present in the original images from which they were derived. Another more versatile alternative is to synthesize liver lesion images using Generative Adversarial Networks (GAN). In [31], Deep Convolutional GAN (DCGAN) was used to synthesize three types of FLLs namely, cysts, MET and HEM. They used both GAN generated images as well as the images produced by transformations to train the DL classifier. The use of GAN enlarged their dataset, improved its variability and also enhanced the performance of the CAD system.

Transfer learning/fine-tuning is another technique adopted to handle the issue of insufficient training data. This approach eliminates the need to train the NN from scratch. Wang *et al*. [36], used transfer learning and reported good classification accuracy with a small dataset. They adopted a 50-layer ResNet pre-trained with

ImageNet and fine-tuned with annotated medical images. AlexNet, GoogLeNet and VGGNet are the other pre-trained networks used in the reviewed literature. Some researchers have employed both transfer learning and data augmentation techniques to improve the performance of the CAD system.

For validation and testing both hold-out [17,20,36,50,105] and CV [19, 21, 63, 52] techniques were used. It can be seen that many researchers used CV technique, although it further increases the training time of DL models, perhaps, to avoid overfitting. Table 8 summarizes the DL-CAD systems in terms of techniques adopted and performance.

Table 8. DL approaches for liver lesion classification.

Although a few papers that dealt with DL based segmentation, had used public databases, it was observed that most researchers used datasets from their collaborating hospitals, making it difficult to assess the efficiency of the systems from a generic point of view. The existing public databases have limited images, are less diverse and are suitable for segmentation evaluation only.

5. Discussion and research gaps

The number of patients with liver diseases is increasing day by day, which is overburdening the radiologists due to the enormous volume of medical images to be analyzed. Hence, the incorporation of CAD systems as an assisting tool for radiologists is essential. However, the CAD systems developed so far have various limitations that have to be overcome to render them suitable in a clinical environment. These shortcomings are discussed below.

To begin with, for the CAD system to be suitable for clinical practice, it should be able to analyze the images acquired in all the phases as the details of some of the lesions may be visible only in certain phases. But only selected phases were considered in most of the published literature. In addition, powerful techniques to capture the dynamic enhancement patterns quantitatively in the different CT phases have not been developed. Few recent studies have explored this aspect, but more comprehensive features have to be discovered.

As mentioned before, some authors have chosen to work only on NECT images, due to the detrimental reactions caused during the acquisition of CECT images (especially for diabetes and kidney patients). Such CAD systems have to focus intensively on preprocessing techniques to make an accurate diagnosis. The work in [42] has shown encouraging results. However, such CAD systems have mainly relied on manual segmentation, which is a tedious task and it also makes the output sensitive to the ROI selected. Hence developing automated/semi-automated methods for segmenting lesions from NECT images is an area open to research.

Another important aspect is to focus on developing simpler and computationally efficient algorithms as the volume of CT data to be processed by the CAD system is already high. Instead of the hierarchical strategy, the lesions can be delineated directly from the abdominal CT image to reduce the computational complexity to some extent. A few researchers of conventional CAD systems have come up with such approaches, but they are mainly semi-automatic and not very effective. Some researchers have performed only liver segmentation and achieved satisfactory classification results. Both these CAD systems can be further investigated for clinical feasibility.

In conventional CAD systems, considerable research is being done to fully automate the segmentation process. However, the shape and appearance of liver and liver lesions are highly variable, hence it is not practical to develop a completely automatic segmentation algorithm. Segmentation methods that can interactively correct the segmentation errors should be developed. The work in [10] demonstrated such an approach, but the number of such interactions must be optimized.

Recent studies have focused on DL algorithms for segmentation. The DL methods are largely robust to noise and poor contrast. Thus eliminating the need for major preprocessing operations. The DL approach can also enable complete automation of the segmentation process. But they may further augment the computational complexity of the CAD systems. Hence approaches to optimize the same have to be explored.

Another critical issue in CAD system development (especially conventional CAD) is selecting the appropriate features that characterize the different classes of liver lesions accurately. The efficacy of various handcrafted features (viz. GLCM, LTEM etc) have been investigated by different researchers. However, the most discriminating features of the specific lesions have not been discovered so far. In the DL-CAD systems, the DL models extract the hidden complex patterns automatically from the input and provide superior diagnosis. Moreover, non-experts with little domain knowledge can also develop these systems since the features need not be explicitly chosen.

Despite the various advantages that the DL-CAD systems offer compared to the conventional CAD systems, they have many downsides. Due to their black-box like characteristics, it is extremely difficult to interpret the DL models which is very essential in medical applications. Although some strategies have been developed to address this issue, they have not been used in the reviewed literature. Hence, in case of errors such as misdiagnosis, debugging becomes difficult as the user has little control over the operations within the DL models. Other issues are the need for highly powerful processing systems, huge volume of annotated data, long training time and computational complexity. The conventional CAD systems do not face these issues. Since both conventional and DL approaches have their own merits and demerits, more research should be directed towards developing hybrid CAD systems that leverage the strengths of the two approaches, instead of relying on only one of them. Such systems will be versatile, transparent, accurate and fast.

Hepatic CAD systems based on unsupervised, semi-supervised and reinforcement learning have not been researched so far, to the best of our knowledge. These CAD systems can be useful in situations where largescale datasets are available, but annotating them is a tedious task. Moreover, such CAD systems may be more efficient and accurate than their supervised learning counterparts.

Other areas that can be investigated to develop advanced systems include integrating essential clinical features of hepatic pathologies along with radiological features. Another area of research could be incorporating multimodal image fusion into the CAD system to improve diagnosis.

A point that needs to be reiterated is that a large public database dedicated to liver diseases especially FLLs should be constructed. The existing public datasets have limited annotated CT images. Hence, private hospital datasets were used in most of the reviewed literature. As a result, it is difficult to compare the performances of the CAD systems. Efforts should be made in this regard, to facilitate quality research in liver disease diagnosis.

The initial hepatic CAD systems were based on manual lesion segmentation, handcrafted features and ML technology. As research progressed in the related fields, better segmentation, feature extraction and ML algorithms were developed, which paved the way for improved CAD systems. More recently, the incorporation of the DL technology has brought about a sea change in hepatic CAD system development, especially with respect to segmentation and feature extraction stages. Nevertheless, further research is needed, to make affordable CAD systems that are accurate, reliable, efficient, robust and clinically viable.

6. Conclusion

This paper discusses the various approaches used for preprocessing, segmentation, feature extraction and classification of hepatic abnormalities, mainly benign and malignant lesions reported in conventional and DL based CAD systems. The methods used for liver lesion segmentation have also been discussed. The purpose of a CAD system is to support a radiologist in the decision-making process by diagnosing the abnormalities accurately and hence giving a second opinion. To be of practical value, they should be able to detect the lesions that may be missed by a radiologist. Even though much research has been done in the last two decades, there is still scope for more research as robust CAD systems that provide high accuracy, high processing speed and a reasonable level of automation, suitable for clinical practice have to be developed.

Declaration of Competing Interest

None declared.

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Contributors

P Vaidehi Nayantara analyzed the papers and drafted the article. Surekha Kamath, Manjunath K.N and Rajagopal K.V revised it critically for important intellectual content. All the authors approved the final version of the manuscript.

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B	M	N	ABN	HCC	HEM	MET	CC	HA	FNH	Cyst	CIRR	ABS	LC	References
√	√													[12–21]
				√	√									[22–24]
		√		√										[25–28]
		√	√											[29,30]
					√	√				√				[31,32]
		√		√	√					√				[33–35]
				√	√				√	√				[36,37]
		√		√							√			[10]
				√		√								[38]
				√	√	√								[39]
√	√	√												[40,41]
		√		√	√	√				√		√		[42]
		√		√			√				√			[43]
		√								√	√		√	[44]
		√			√					√			√	[45]
				√	√		√	√						[46]
						√				√				[47]
					√	√				√				[48]
				√										[49–51]
						√								[52]

Table 1. Categories considered for classification in the reviewed CAD systems.

FLL	Radiographic features		References
	NECT	CECT	
Cyst	Well-defined lesions of water attenuation that do not enhance after administration of contrast material.		[56,57]
HEM	Hypo- or isodense to liver parenchyma.	Discontinuous peripheral nodular enhancement in the ART phase with progressive centripetal filling-in in the PV and DLY phases.	[57,58]
FNH	Isodense or minimally hypodense mass of homogeneous density, a central scar of low density seen in 30% of cases.	Homogeneously enhances in ART phase, central scar remains hypodense. Attenuation difference between liver and lesion decreases and becomes isodense in PV and DLY phases.	[4,56,58,59]
METS	Can be of variable density depending on size, vascularity, etc. Majority are hypodense with Hounsfield Unit (HU) values between that of water and normal liver.	Best seen during the portal phase.	[56]
HCC	Mostly hypo- or isodense.	Enhances avidly in the ART phase, becomes iso/hypodense with the liver parenchyma in the PV phase and shows most lesions as hypodense compared with surrounding liver in the DLY phase.	[4]

Table 2. Typical radiographic features of common liver lesions from other studies.

Phases					References
NECT	ART	PV	DLY	EQ	
√	√	√			[12, 36–38, 43, 60]
√					[14,15,18,33–35,42]
		√			[31, 32, 48, 50,61]
√	√	√	√		[10, 45, 62]
√	√		√		[63]
	√	√		√	[51]
	√	√	√		[49]
	√				[27]

Table 3. Summary of the CT phases employed in the reviewed papers.

Liver segmentation	Lesion segmentation	Inferences	References
Thresholding + Morphological erosion + Automatic region growing	FCM	• Determining the exact liver intensity range is difficult. • All types of peripheral lesions may not get detected due to initial thresholding.	[66]
Semiautomatic region growing	Nil	• Interactively corrects segmentation errors. • User interventions required may be large, when errors are present in many slices.	[10]
NFB feature bit map + region growing + deformable contour model	Nil	• Complex algorithm. • May result in incorrect classification results if liver is incorrectly segmented, since no lesion segmentation.	[24]
Neutrosophic domain + FCM clustering	Nil	• Neutrosophy gives good segmentation results for images with blurry edges.	[29]
Neutrosophic domain + Adaptive thresholding + Morphological operations + Watershed algorithm	Fast FCM	• Over-segmentation reduced. • Good results with non-uniform CT images.	[65]
Kirsch filter + Concave and Convex points identification + mean shift algorithm + FCM	FCM	• Liver and lesions with vague boundaries segmented well.	[70]
Histogram analysis + thresholding + morphological operations	FCM + automated region growing	• May miss peripheral lesions.	[18]
Nil	Seeded region	• Seed selection is difficult.	[69]

	growing	• Segmented output sensitive to selected seed point	
Histogram analysis + thresholding + morphological operations	FCM	• May miss peripheral lesions. • Same morphological operations may not suit all segmented results.	[13, 30, 38, 46]
FCM	Region growing	• High computation time.	[77]
Marker controlled watershed algorithm	GMM	• May not be effective when adjacent organs have similar intensities.	[39]
Nil	Semiautomatic region growing	• Delineated lesion output sensitive to user input. • Requires user to identify the lesion and input seed point.	[12]
Adaptive thresholding	Adaptive thresholding	• Computationally inexpensive. • Less robust.	[30]
FCM + Grey wolf optimization	Fast FCM clustering	• The local minima convergence issue of FCM addressed.	[16]
Nil	DRLSE + Region growing	• Can delineate lesions of complex topology.	[45]

Table 4. Summary of the liver and/or lesion segmentation methods used in the reviewed literature.

Methods	Pros	Cons
Thresholding	Produces good results for homogeneous images with high contrast.	Selection of threshold is difficult. Not suitable for images with peripheral liver lesions.
Region growing	Simple concept. Regions with same properties are segmented well.	Sensitive to noise and seed point.
Watershed	Automatic and fast algorithm.	Does not produce good results when the boundary between organs are blurred.
FCM	Robust algorithm. Comparatively better results with noisy images.	High computational complexity.
Active contour models	Dynamically adapt in their search for minimal energy.	Require initial contour to be defined and higher computation time.

Table 5. Pros and cons of the prominent segmentation algorithms.

Technique	References
GLCM	[13, 16, 18, 22–26, 29, 33-35, 39, 40, 42–45, 51]
Histogram based	[10, 18, 26, 33, 34, 40, 42, 43, 45, 51]
Run length Matrix	[43]
Local binary pattern	[27, 40]
Fractal based	[18, 24, 33, 34, 43]
LTEM	[33, 34, 43, 51]
Wavelet based	[13, 18, 22, 46]
Contourlet based	[22]
SFTA[1]	[30, 40]
FDCT[2] based	[13]
GLDM	[33, 34]
LBP + Histogram Fourier Transform based	[38]
Auto-covariance features	[14, 15]

Table 6. Summary of the commonly used feature extraction techniques.

[1] *Segmentation based Fractal Texture Analysis*
[2] *Fast Discrete Curvelet Transform*

References	Sample size	Extracted features & feature selection technique	Classifier	Performance
[10]	N:14, CIRR:12, HCC:14	Histogram & temporal features	Cascade of LR & SVM	Accuracy (LR):92.5%, Accuracy (SVM):86.9%
[39]	HEM:75, HCC:75, MET:75	Statistical, geometric & GLCM based	DNN	Accuracy:99.4% Sensitivity:100% Specificity:99.1%
[29]	N:30, ABN:30	GLCM based	SVM	Accuracy:95%
[38]	HCC:63, MET:60	LBP Histogram Fourier features	C45	Accuracy:95%
[25]	N:10, HCC:10	GLCM based	NB	Accuracy:95%
[42]	N:105, HCC:134, HEM:110, Cyst:103, MET:77, ABS:105	GLCM based	SVM	Accuracy:93%
[40]	N:62, B:392, M:308	GLCM Based	Ensemble	Accuracy:100%
[12]	B:49, M:22	Texture, shape & Kinetic curve features + Backward elimination	LR	Accuracy:81.7% Sensitivity:81.8% Specificity:81.6%
[27]	N:125, HCC:77	LBP, Legendre moments + Sequential algorithm	Euclidean distance classifier	Accuracy:96.2%

[22]	HCC:150, HEM:150	Contourlet texture features + PCA	PNN	Accuracy:96.7% Sensitivity:97.3% Specificity:96%
[23]	HEM:50, HCC:50	GLCM based	Pulse coupled NN	Accuracy:87% Sensitivity:86 Specificity:88%
[30]	N:20, ABN:60	SFTA features	SVM	Accuracy: 92.5%
[18]	B: 247, M:240	Shape, texture & boundary features.	Ensemble	Accuracy: 98.6%
[45]	N:81, Cyst:38, LC:38, HEM:39	FOS, GLCM, Time series + PCA	Cascaded SVM classifiers	Accuracy:99.5% (N & ABN), 97.4% (cyst & non-cyst), 93.5% (LC & HEM)
[16]	62 CT images	GLCM based	SVM	Accuracy: 97%
[26]	N:231, HCC:464	FOS & GLCM based	SVM	Accuracy: 86.4%
[43]	N:537, CIRR:433, CC:222, HCC:319	LTEM, RLM, COM, GLDM, Fractal and FOS based	AdaBoostM1+J48 in Weka	Accuracy ≈ 90%
[14]	B:84, M:80	Auto-covariance coefficients	SVM	Accuracy= 81.7% Sensitivity=75% Specificity=88%
[33]	N:76, Cyst:19, HEM:28, HCC:24	FOS, GLCM, GLDM, LTEM, Fractal based	Ensemble	Accuracy = 85%

[24]	Hepatoma:20, HEM:10	GLCM based	PNN	Accuracy: 83%
[28]	N: 250, HCC:200	Zernike moment features	Nearest mean classifier	Accuracy(N):98.3% Accuracy(HCC):90.7%
[35]	N:76, Cyst: 19, HEM:28, HCC:24	GLCM based	Cascaded NN classifiers	Accuracy: 97%
[46]	Hepatoma: 40, HEM:30	Wavelet based	PNN	Accuracy: 90.2%
[34]	N:76, Cyst: 19, HEM:28, HCC:24	FOS, GLCM, GLDM, LTEM, Fractal based + GA	Ensemble	Accuracy: 90.6%
[78]	Cyst: 45, MET: 45, HEM: 18, HCC: 11, FNH: 5, ABS: 3, Neuroendocrine neoplasms: 3, Fat: 1, Laceration: 1	Matching metric	SVM	Accuracy < 90%

SFTA: Segmentation based Fractal Texture Analysis, FOS: First Order Statistics, RLM: Run Length Matrix, COM: Co-Occurrence Matrices, FDCT: Fast Discrete Curvelet Transform, DNN: Deep NN.

Table 7. Overview of the CAD systems in terms of sample size, feature extraction & selection techniques, classification methods and performance.

Sample size	**Liver/lesion segmentation**	**Feature extraction & classification**	**Performance**	**References**
B:100, M:100	Nil	CNN + ELM	Accuracy: 97.3%	[19]
N: 227, Cyst:293,	Liver: Iterative probabilistic	DADRN	Accuracy: 86.9%	[106]

FNH: 130, HCC: 251, HEM: 190	atlas model			
Cyst: 119, FNH: 71, HCC: 103, HEM: 95	Manual	ResNet	Accuracy: 91.2%	[36]
B: 56, M:56	Nil	CNN+DWT+LSTM	Accuracy: 99.1%	[21]
Diffuse HCC:46, Nodular HCC: 43, Massive HCC:76	FCN	CNN	Accuracy: 98 %	[50]
Cyst: 110, FNH:114, HCC: 132, HEM:124	Random walk-based interactive segmentation	ResGLNet + BD-LSTM + SVM	Accuracy: 90.9%	[37]
Cyst: 53, MET: 64, HEM: 65	Manual	CNN	Sensitivity: 85.7 % Specificity: 92.4%	[31]
Cyst: 115, MET:115	FCN	InceptionV3 + residual connections	Accuracy: 0.96	[47]

ELM: Extreme Learning Machine, DADRN: Dual Attention Dilated Residual Network

Table 8. DL approaches for liver lesion classification.

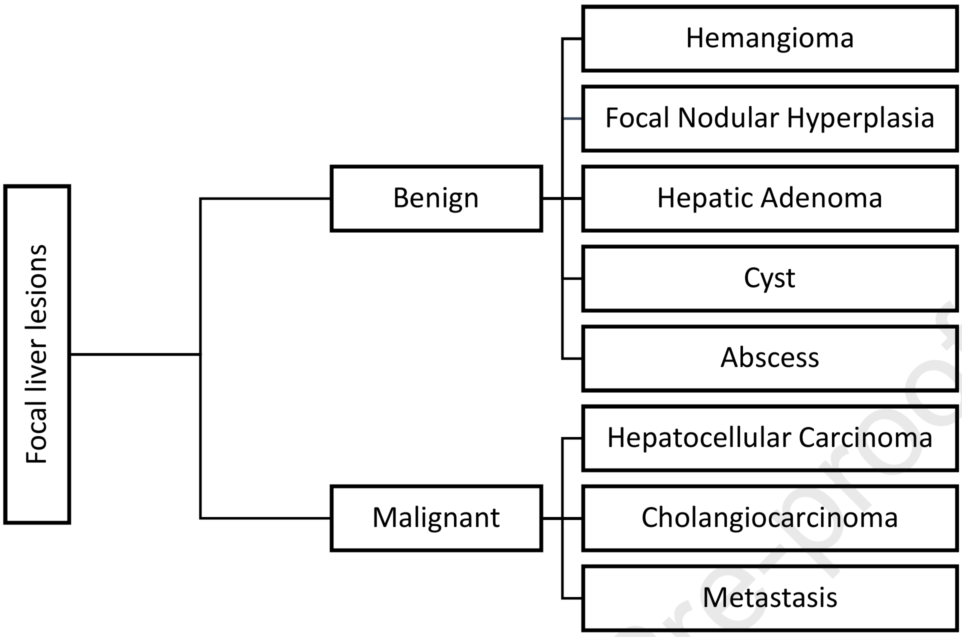
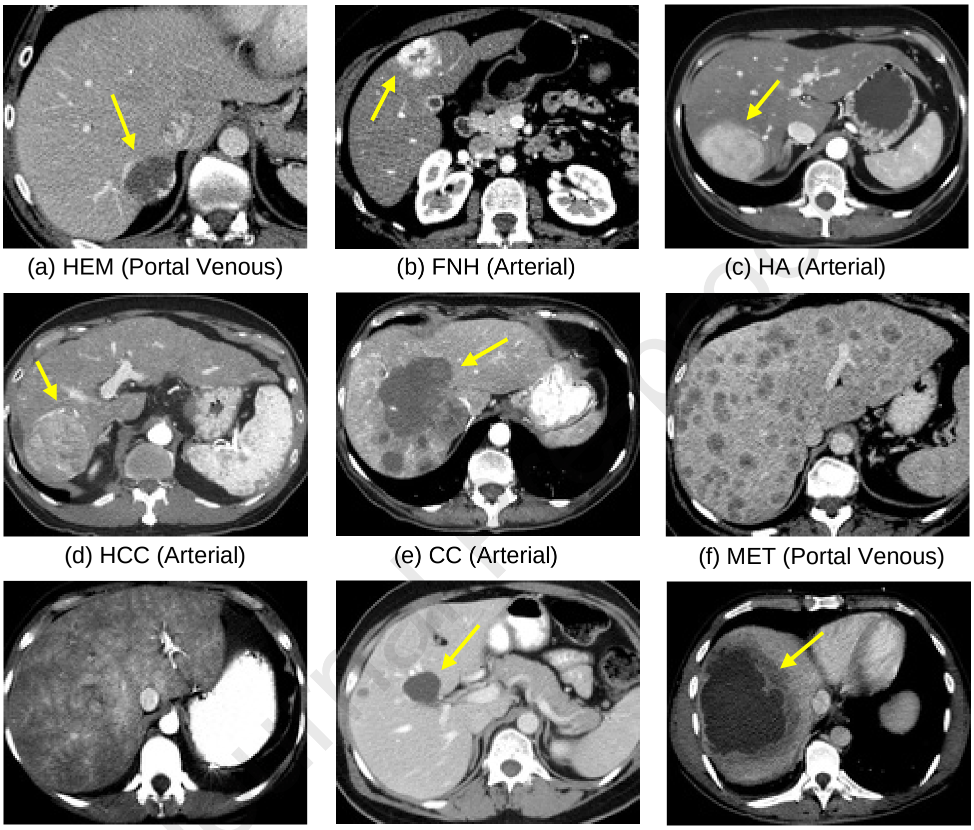


Fig. 1. A pictorial description of the FLLs considered in the reviewed papers.



(a) HEM (Portal Venous) (b) FNH (Arterial) (c) HA (Arterial)

(d) HCC (Arterial) (e) CC (Arterial) (f) MET (Portal Venous)

(g) Cirrhosis (Portal Venous) (h) Cyst (Portal Venous) (i) Abscess (Portal Venous)

Fig. 2. Abdominal CT images indicating the liver anomalies along with the phase [11] (arrows were not shown in original images. For sake of explanation we have included them).

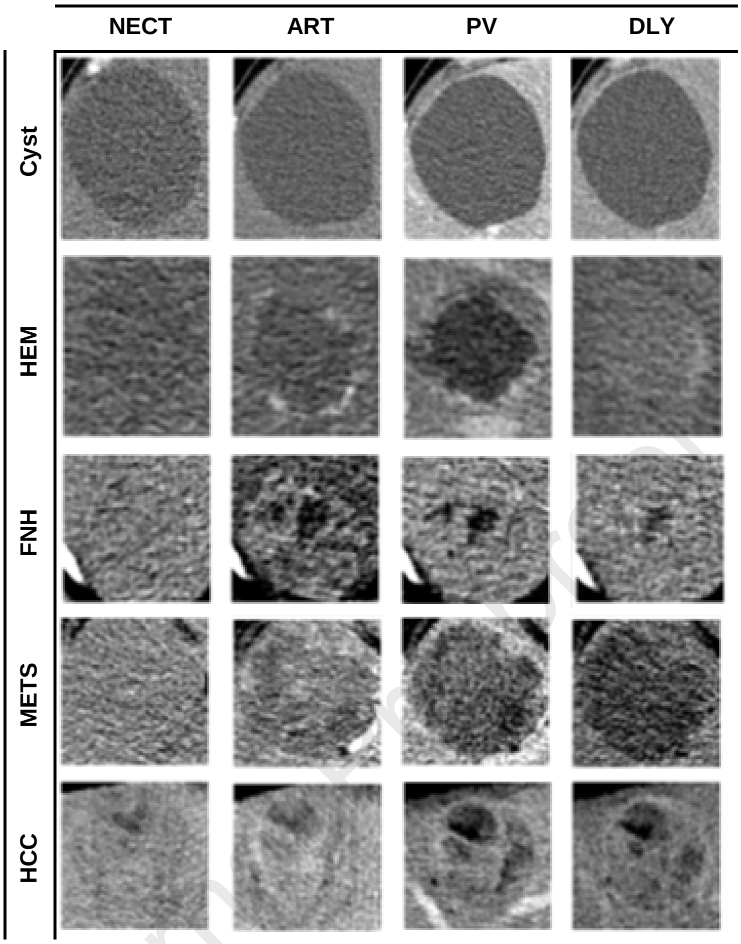


Fig. 3. Visualization of common liver lesions (on axial CT) in NECT, ART, PV and DLY phases (adapted from [55]).

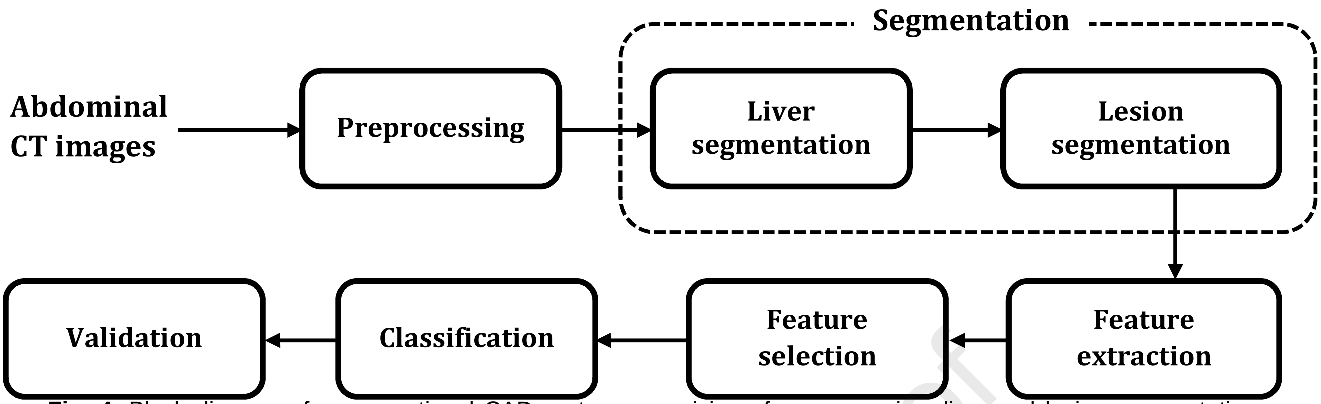


Fig. 4. Block diagram of a conventional CAD system comprising of preprocessing, liver and lesion segmentation, feature extraction, feature selection and classification stages.

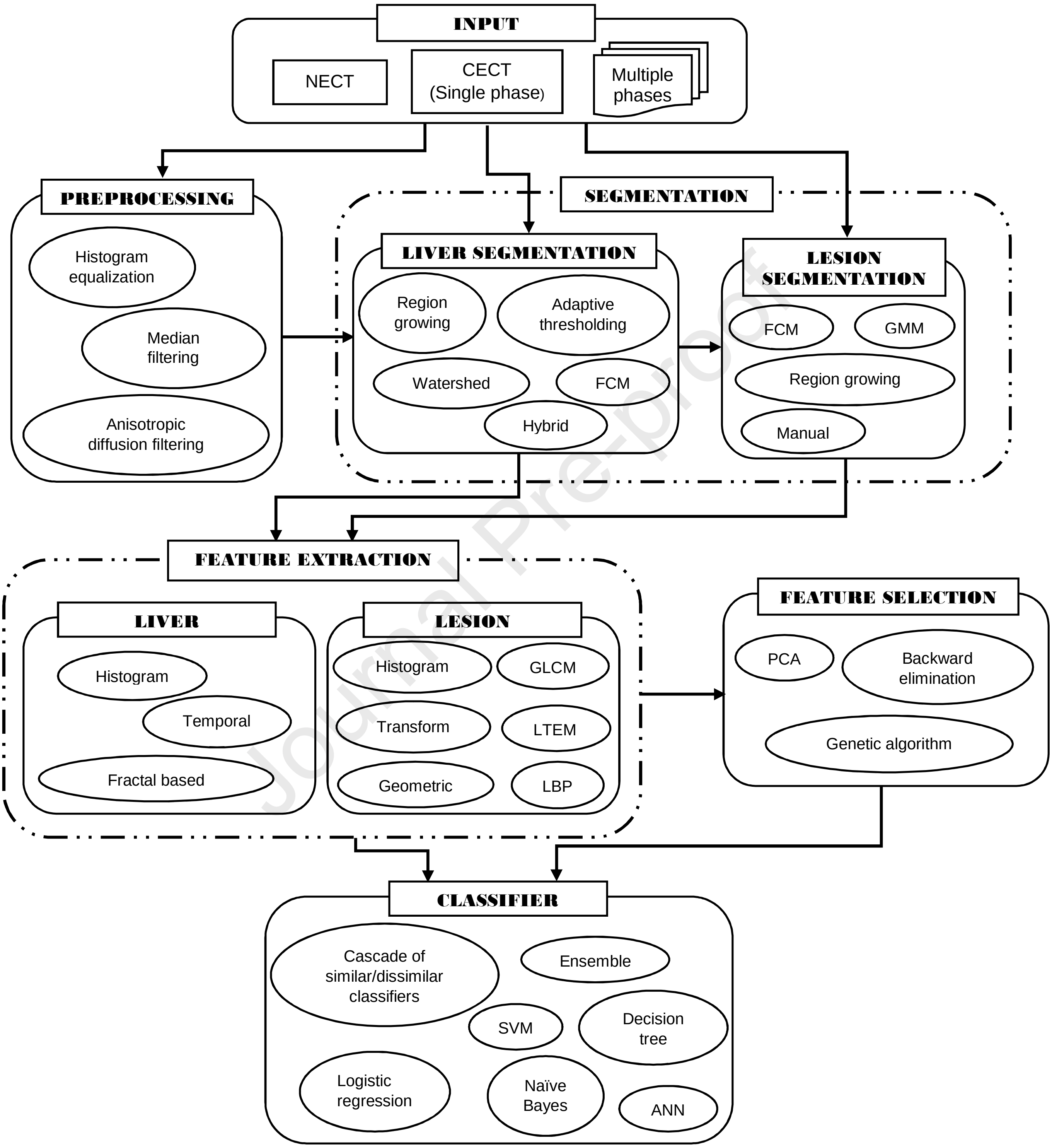
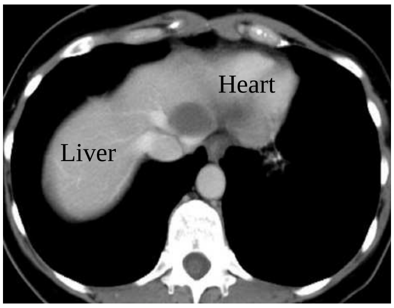
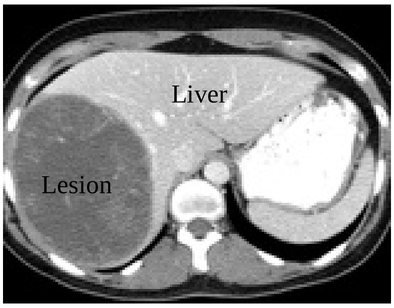

INPUT
NECT
CECT
(Single phase)
Multiple
phases
PREPROCESSING
Histogram
equalization
Median
filtering
Anisotropic
diffusion filtering
SEGMENTATION
LIVER SEGMENTATION
Region
growing
Adaptive
thresholding
Watershed
FCM
Hybrid
LESION
SEGMENTATION
FCM
GMM
Region growing
Manual
FEATURE EXTRACTION
LIVER
Histogram
Temporal
Fractal based
LESION
Histogram
GLCM
Transform
LTEM
Geometric
LBP
FEATURE SELECTION
PCA
Backward
elimination
Genetic algorithm
CLASSIFIER
Cascade of
similar/dissimilar
classifiers
Ensemble
SVM
Decision
tree
Logistic
regression
Naïve
Bayes
ANN

Fig. 5. A pictorial overview showing the workflow adopted and prominent techniques used in the reviewed conventional CAD systems.

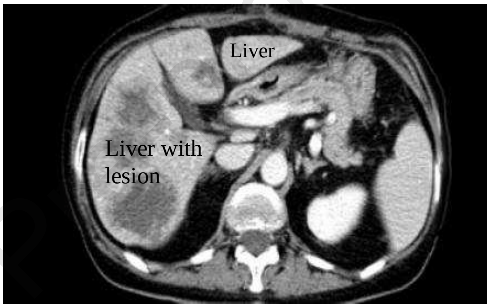


(a) Vague boundary between organs [11].

(b) Change in liver morphology due to the lesions[11].

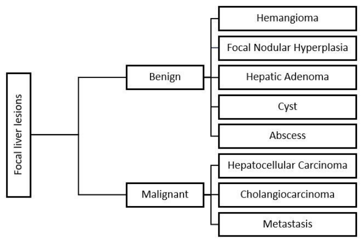


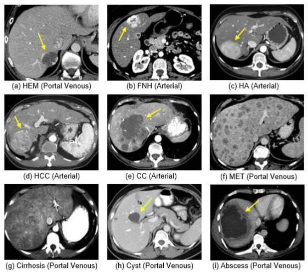
(c) Peripheral hepatic lesion [11].

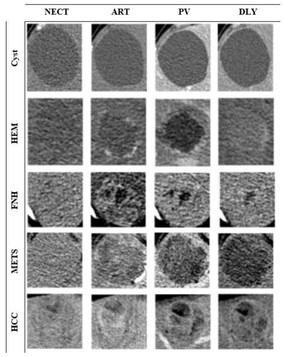


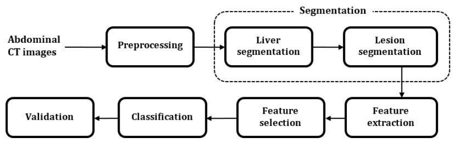
(d) Division of liver into two lobes [54].

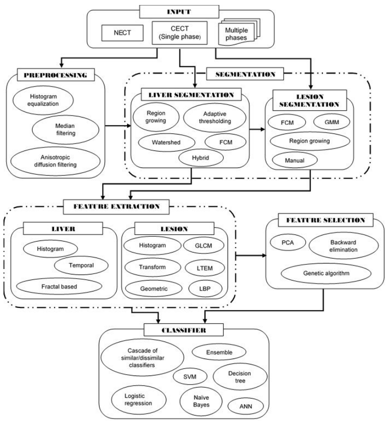
Fig. 6. CT images showing difficulties associated with liver segmentation [11] (labels were not shown in the original images. For the sake of explanation we have included them)

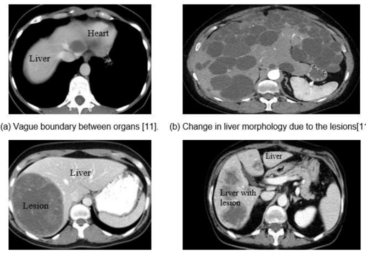

Focal liver lesions
Benign
Malignant
Hemangioma
Focal Nodular Hyperplasia
Hepatic Adenoma
Cyst
Abscess
Hepatocellular Carcinoma
Cholangiocarcinoma
Metastasis


(a) HEM (Portal Venous)
(b) FNH (Arterial)
(c) HA (Arterial)
(d) HCC (Arterial)
(e) CC (Arterial)
(f) MET (Portal Venous)
(g) Cirrhosis (Portal Venous)
(h) Cyst (Portal Venous)
(i) Abscess (Portal Venous)


NECT
ART
PV
DLY
Cyst
HEM
FNH
METS
HCC


Segmentation
Abdominal
CT images
Preprocessing
Liver
segmentation
Lesion
segmentation
Feature
extraction
Feature
selection
Classification
Validation


INPUT
NECT
CECT
(Single phase)
Multiple
phases
PREPROCESSING
Histogram
equalization
Median
filtering
Anisotropic
diffusion filtering
SEGMENTATION
LIVER SEGMENTATION
Region
growing
Adaptive
thresholding
Watershed
FCM
Hybrid
LESION
SEGMENTATION
FCM
GMM
Region growing
Manual
FEATURE EXTRACTION
LIVER
Histogram
Temporal
Fractal based
LESION
Histogram
GLCM
Transform
LTEM
Geometric
LBP
FEATURE SELECTION
PCA
Backward
elimination
Genetic algorithm
CLASSIFIER
Cascade of
similar/dissimilar
classifiers
Ensemble
SVM
Decision
tree
Logistic
regression
Naive
Bayes
ANN



(a) Vague boundary between organs [11]. (b) Change in liver morphology due to the lesions[11].

(c) Peripheral hepatic lesion [11]. (d) Division of liver into two lobes [54].

Highlights

- A comprehensive review of conventional and deep learning based CAD systems for liver lesion diagnosis.
- Provides an overview of the various technical as well as medical aspects associated with hepatic lesion diagnosis.
- The articles published in the last two decades were analyzed in the review.
- The various limitations of the current systems along with directions for future research are outlined.

Conflict of interest statement

None declared.