

# An approach for liver cancer detection from histopathology images using hybrid pre-trained models

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## ABSTRACT

Histopathological image analysis (HIA) plays an essential role in detecting cancer cell development, but it is time-consuming, prone to inaccuracy, and dependent on pathologist competence. This paper proposes an automated HIA that uses deep learning to improve accuracy and efficiency in liver cancer cell growth. The model uses whole slide image (WSI) input, open computer vision (OpenCV) libraries for image preprocessing, ResNet50 for patch-level feature extraction, and multiple instances learning for image-level classification. The suggested approach accurately distinguishes liver histopathological pictures as cancerous or non-cancerous. Assisting in the early detection of liver cancer cell development with potential invasion or spread.

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## 1. INTRODUCTION

According to “the American Cancer Society”, concerning 41,210 additional instances of primary cancers of the liver and intrahepatic bile duct cancer will be detected in 2023 (27,980 men and 13,230 women), with approximately 29,380 people (19,000 men and 10,380 women) dying from these malignancies. The death rate from liver cancer has nearly doubled since 1980 [1], while the number of cases has nearly tripled. As obesity and type 2 diabetes mellitus epidemics spread throughout the world and in India, nonalcoholic fatty liver disease (NAFLD) is considered one of the leading causes of persistent liver cancer, and its prevalence is expected to rise. The current international guidelines for NAFLD do not fully address the situation in India due to cultural differences and healthcare infrastructure variations. The research underlines the importance of identifying those at risk of developing progressive liver disease to increase referrals and guide optimal care. Based on consensus-based recommendations, the study concludes with NAFLD’s nomenclature, diagnosis, and management customized specifically for the Indian context [2].

The manual pathology of liver cancer, on the other hand, need a great deal of time and effort in order for it to be accurate. It is necessary for a competent pathologist to use a microscopy device to determine the presence of cancerous cells in an image in order to obtain an appropriate diagnosis based on a visual inspection of images. The process of analyzing a whole slide image (WSI) could take a pathologist up to

thirty hours in order to identify the particular tumor cell down to the specific stage of the cancer cell. It will be critical in the future to establish speedy and dependable pathology screening technology.

In recent years, deep-learning image application classification has attained extremely high accuracy. The use of deep learning algorithms in the classification of histopathology images has gained prominence in digital pathology in recent years due to recent advances in the field of deep learning. Bhaskar *et al.* [3] applied U-net and convolutional neural network (CNN) models on lung computed tomography (CT) images to classify lung cancer and achieved 96% accuracy. Using the ResNet architecture, Gothane *et al.* [4] classified the fundus images with an accuracy of 82%. Tiwari *et al.* [5] investigated the reliability of a deep learning system for diagnosing lung disease based on clinical image analysis challenges. Using multiscale Laplacian of Gaussian filters, dimensions, and structure restrictions, Bhaskar and Ganashree [6] identified nodule candidates.

Deep learning-based classification of images in histopathology is being used in hepatocellular carcinoma (HCC) diagnosis. By adapting labelled histology pictures from multiple disciplines (tissue categories), Xia *et al.* [7] address the shortage of labelled training datasets in histopathology pictures of a specific area. The dataset from different tissue categories was employed to pre-train CNNs, and the accuracy was 84.3% vs 78.3%, with an area under the receiver operating characteristic curve (AUC) of 0.918 vs 0.867 [7]. Using the SENet deep learning network, Chen *et al.* [8] demonstrated a 95.27% accuracy in classifying all kinds of distinguished liver cancer histopathology images. The binary classifier developed by Lin *et al.* [9] classified HCC histopathological images with 91.37% accuracy, 92.16% sensitivity, and 90.57% specificity.

HCC diagnosis also makes use of deep learning-based histopathological H&E classification of images. Lal *et al.* [10] published NucleiSegNet, a powerful deep-learning network for nuclei segmentation in H&E-stained liver cancer histopathology images. Inception V3 was trained using histopathological H&E images by Chen *et al.* [11] with 96.0% accuracy.

HCC is also diagnosed using deep learning-based CT image classification. Othman *et al.* [12] used CNNs and achieved 99.5% accuracy, 0.864 precision, and 0.979 recall. Li *et al.* [13] used an approach that used a genetic algorithm with a CNN to categorize liver CT images, which may be separated into two groups: cancerous and non-cancerous. In order to detect liver tumours, B *et al.* [14] used an AE-ELM network and outperformed CNN and ELM models in terms of accuracy. As a theoretical solution to the problem of liver cancer, Dong *et al.* [15] introduced the hierarchical fusion CNN (HFCNN) for liver tumour segmentation.

Deep learning has been used to save time while still accurately predicting tumours. Deep learning outperforms three expert radiologists in identifying liver tumours into seven categories, according to a study published in frontiers in oncology. Using enhanced images, CNN distinguishes benign from malignant liver tumours [16].

## 2. PROPOSED METHOD

The suggested approach to classifying liver cancer histological images employing global labels (image-level labels) is limited since tagged liver cancer histopathological images are accessible. As a result, patch features are extracted using a pre-trained network. The feature is then constructed by picking positive and negative instances from the data. A four-step method is illustrated in Figure 1: first, WSI is preprocessed; then, patch-level features are combined to create an image-level feature descriptor; third, discriminative characteristics are chosen to produce the ultimate WSI characteristics; and lastly, liver cancer CT images from histopathology are identified as malignant or non-cancerous.

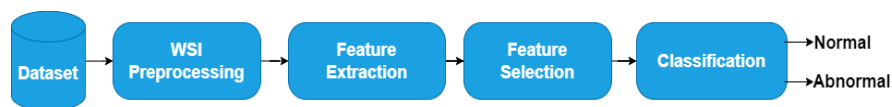


Figure 1. Proposed method

Figure 1 describes a proposed method for categorizing liver histopathology images as either abnormal or normal, based on whether the images appear abnormal or normal. According to the proposed approach, liver histopathology images can be classified according to whether the images are normal or abnormal according to whether the images appear normal or abnormal. Thus, it becomes possible to detect liver cancer cells well in advance of their invasion or spread from one organ to another, thus enabling the detection of liver cancer cells at an early stage.

### 3. IMPLEMENTATION

Figure 2 depicts a work implementation that inputs WSI and preprocesses the images using open computer vision (OpenCV) resources [17]. To extract the WSI patch-level characteristics, transfer learning with ResNet50 is employed. To provide final image-level classification features, these attributes are integrated with multiple instance learning (MIL).

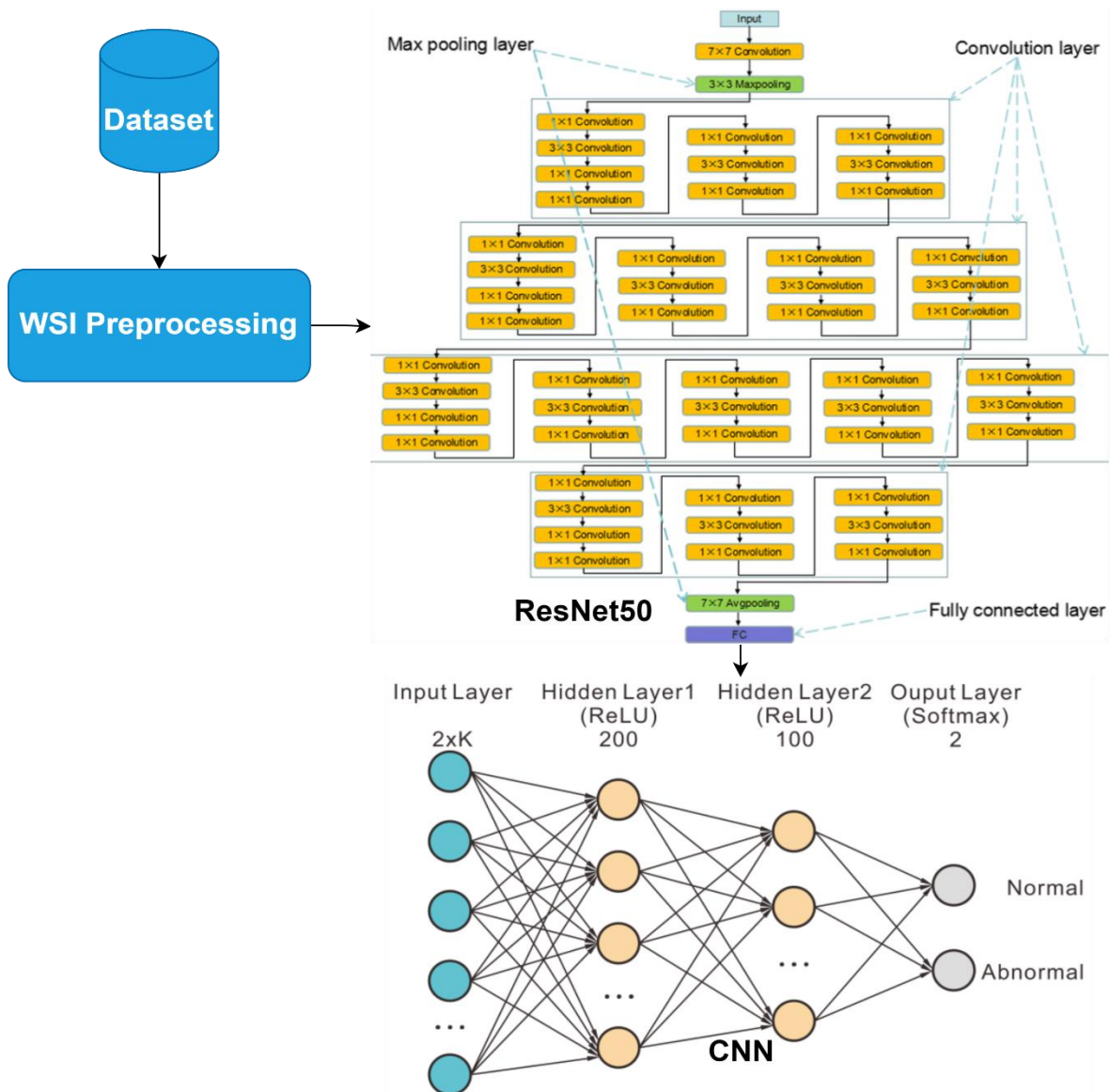


Figure 2. Architecture

#### 3.1. Datasets

##### 3.1.1. The cancer genome atlas

The researchers in this work evaluated a classification approach for liver hepatocellular carcinoma using WSIs retrieved from The cancer genome atlas (TCGA) [17]. Figure 3(a) depicts a total of 462 liver CT scans, 79 of which are non-cancerous and 383 of which are malignant. The slides were scanned at 20 $\times$  magnification and analyzed at 0.5  $\mu\text{m}/\text{pixel}$  fixed zoom. The TCGA dataset contains annotations indicating the various kinds of WSIs but no annotations for precise segmentation of liver cancer tissue areas. As a result, the universal annotations were employed as the study's ground truth. As shown in Figure 3(b), the researchers separated the histopathological pictures into three datasets: a training dataset (70%), a validation dataset (15%), and a testing dataset (15%). These images averaged over 15,000 pixels in width and exceeded 100,000 pixels in height, as shown in Figure 3(c). The images could not be directly input into the CNN.

According to Figure 3(d), segments were created from WSIs using the OpenSlide package [18]. The number of patches extracted varied according to WSI size, with most pictures comprising around 300 patches and some including over 2,000 patches. The researchers collected 189,531 patches for the study in total.

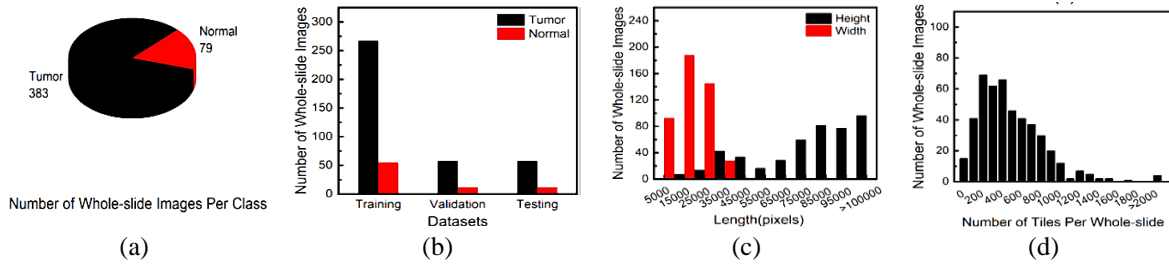


Figure 3. TCGA dataset; (a) WSIs class labels, (b) WSIs separation for training, testing, and validation, (c) image size distribution, and (d) the number of patches distributed in each slide [17]

**3.1.2. The liver tumor segmentation benchmark**

Bilic *et al.* [19] published a joint study at IEEE International Symposium on Biomedical Imaging (ISBI) 2017 and the International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2017. ISBI 2017 hosted a study entitled liver tumor segmentation benchmark (LiTS), which was a benchmark for liver tumor segmentation. The results of this benchmark were summarized in this paper. It was developed in association with seven hospitals and research institutions across North America and has been designed to produce images ranging in size and appearance from hyper- to hypo-dense. In this paper, 75 liver segments and 131 CT volumes obtained from different patients were used to train and test 75 liver segments and 131 tumor segments using unrevealed CT images.

**3.2. WSI preprocessing**

There are a number of steps involved in the process of preprocessing slides from the SVS format in order to be able to analyze WSIs that are saved as whole slide images. This process involves some multiple steps, and requires a number of resources. Firstly, the images are converted to the PNG format, and then they undergo a variety of processing steps in order to be ready for use once they have undergone the necessary processing steps to be ready to be used once they have been converted.

The initial step involves converting the image from the default blue, green, red (BGR) format to the hue, saturation, value (HSV) format using the OpenCV library [20]. Otsu’s thresholding technique [21] is then applied to the hue and saturation layers of the HSV image. This technique is used for image segmentation, allowing changes to the pixels of the image for easier analysis. The resulting masked layers of H and S are merged to obtain the final threshold image.

It is then transformed into the LAB format, a system for representing colours that describes the lightness of the image as L, the green-red values as A, and the blue-yellow values as B. CIELAB is intended to simulate human vision perception [22]. The adaptive histogram equalization algorithm performs colour normalization [23] on the layer, specifically on the LAB picture. This procedure tries to eliminate stains from tissue slide imaging caused by the H&E technique. Finally, as represented in Figure 4, the image is transformed back to RGB format.

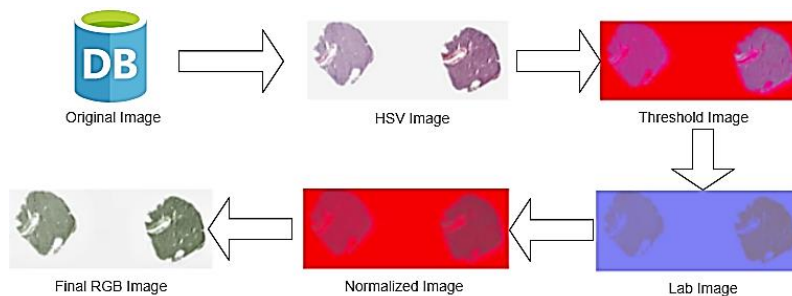


Figure 4. Image processing flow chart for slide images

As a result of the presence of background in most WSI regions, the tissue regions must be extracted for further analysis as they contain a considerable amount of background. The image is segmented into  $224 \times 224$  patches and patches containing at least 50% tissue are evaluated for their amount of tissue content. In order to further process these selected patches, the selected patches are then fed into the ResNet50 model for further processing.

The OpenCV library [20] is used throughout the entire process of preprocessing images, since it contains most of the necessary functions. In addition to the libraries mentioned in the article which can be used in the preprocessing process, a variety of other libraries are also listed that could also be used for the preprocessing process, such as pillow and openslide [18]. These libraries can be used in addition to the ones mentioned in the article.

### 3.3. Extraction of features

There are several ways in which an extraction operation can be executed on a dataset. As a result, an extraction operation can be used to reduce the number of features within the dataset by creating new features from those that already exist following a previous operation. As a result, the overall number of features in the dataset can be reduced. Because the amount of information is expected to decrease over time, it is likely that most of the information in the original characteristic set will be compressed as a result of this condensing of the information, as most of the information in the original characteristic set is likely to be compressed.

It is not possible to detect tumors in slide photos by manually adding characteristics. As a result, as shown in Figure 5, He *et al.* [24] propose extracting characteristics from images employing transfer learning, specifically a CNN termed ResNet50. This 50-layer network has been pre-trained on over a million images from the ImageNet database. The authors change the network, which is normally used for classification, by eliminating the fully connected layer and making the trainable parameters false. It enables them to obtain patch vectors with the required categorization information.

As a method for obtaining an image-level feature vector, the authors employ a method called multiple-instance learning. This process involves the aggregation of patch-level feature vectors that have been obtained during the transfer learning process. A study conducted by the authors finds that this feature aggregation model improves the accuracy of liver cancer classification by combining several features. In order for the aggregation to take place, some form of p-norm pooling is used, more specifically  $p = 3$ .

$$f_p(v) = \left( \frac{1}{N} \sum_{i=1}^N v_i^p \right)^{\frac{1}{p}} \quad (1)$$

$N$ : number of patches.

$v_i^p$ : feature vector of the  $i^{th}$  patch.

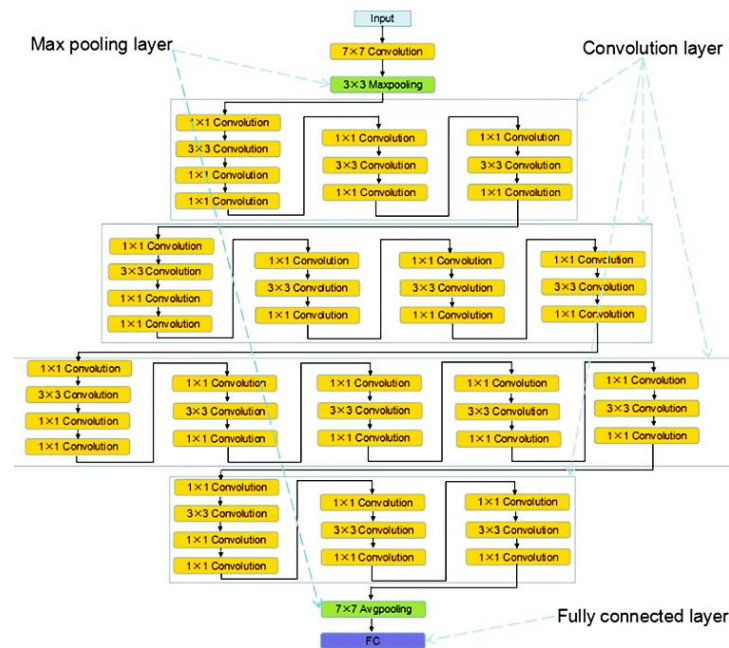


Figure 5. Architecture of ResNet50

### 3.4. Feature selection

The authors recommend that only a few well-chosen and appropriate features be used to distinguish between malignant and non-cancerous liver tissue sections. As illustrated in Figure 6, they use MIL approaches to generate image-level feature descriptors from patch-level data, which is CNN. From the aggregated features, a vector of size  $2048 \times 1$  is constructed, and the top and bottom  $k$  values are chosen, with  $k$  set to 104.

#### 3.4.1. Convolutional neural network

To investigate the interactions between the selected features, a multilayer perceptron CNN is employed as the final classifier and is made up of 2-fully connected layers, each with two hundred neurons. The activation function of the ReLU is chosen. An output layer with two neurons and the softmax activation function is utilized to identify whether the input images are cancerous or non-cancerous.

#### 3.4.2. Training

The CNN's initial fully linked layers are trained using L2 regularization and dropout techniques at a rate of 0.4 to incorporate regularization and dropout techniques into any single layer. We optimize the binary cross entropy loss function with 24 batches and 0.001 learning rate with 24 batches using the Adam optimizer. To improve classification performance, ten ensemble models with various weights are trained to improve the classification performance, and the identification of a histopathological image is generated by taking the mean of the identifications made by these ten ensemble models.

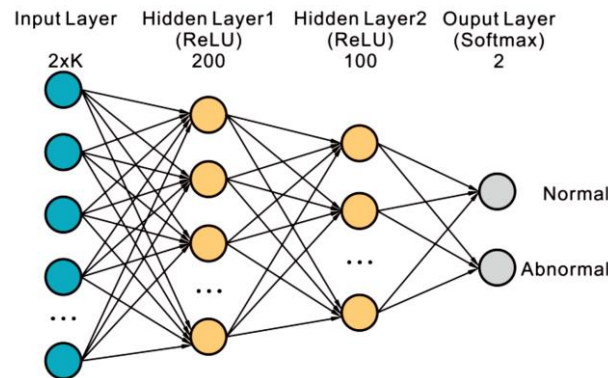


Figure 6. Convolutional neural network architecture

#### 3.4.3. Performance measure

This study focuses on evaluating the accuracy of an algorithm based on its efficiency in classifying datasets by using the validation dataset as a testing environment to evaluate the efficiency of the algorithm. This evaluation is based on the efficiency of the validation dataset. In order to be able to assess the accuracy of the proposed approach, we compare the predictions that were derived from the liver histopathology images with the actual ground truth images that were obtained from the liver tissue in order to be able to measure its precision.

As a result of the four different types of statistics used in the estimation of accuracy, it is vital to understand that: TP represents true positives, FP represents false positives, FN represents false negatives, and TN represents true negatives. These performance indicators are used to assess categorization performance. Using breast cancer histopathology images, precision is measured by dividing accurate cancerous images by anticipated cancerous images. The proportion of properly identified cancerous images divided by the total number of actual cancerous images is employed to estimate recall, or TP.

When the dataset of liver histopathology pictures changes, the receiver operating characteristic (ROC) curve is utilized as an estimation metric, it is often used to evaluate the results of medical image processing. Using the Python module sklearn [25], the  $F_1$ -score is also obtained for binary classification. As opposed to just improving the recall, it rewards strategies that improve both precision and recall at the same time as opposed to improving one at a time. The AUC is more sensitive to data imbalance than the  $F_1$ -score.

$$recall = \frac{TP}{TP+FN} \quad (2)$$

$$precision = \frac{TP}{TP+FP} \quad (3)$$

$$accuracy = \frac{(TP+TN)}{TP+TN+FP+FN} \quad (4)$$

$$F_1\text{-score} = \frac{2 \times precision \times recall}{precision + recall} \quad (5)$$

## 4. RESULTS AND DISCUSSION

### 4.1. Effect of $K$ value selection

This work describes a strategy for classifying liver histopathology pictures that combines transfer learning and MIL. As a result of the use of transfer learning, patch features from images are extracted, and an image-level feature is generated by using MIL to extract the patch features from images. Figures 7(a)-(b), presents how various  $K$  values were evaluated and compared for classification results based on a validation dataset of 70 liver histopathology images and a dataset of different  $K$  values was utilized for the purpose of comparing the results from the study when using a dataset of different  $K$  values.

The outcomes demonstrate that accuracy and F1-score values improve from  $K = 5$  to  $K = 100$  and then decline until  $K = 200$ . As per the results depicted in Figure 7(c),  $K = 100$  yields the greatest results, with an F1-score of 0.99 and an accuracy of 0.986, representing a 13% and 12.6% improvement over  $K = 10$ . As shown in Figure 7(d), after  $K$  is adjusted to 200, the classification findings fall by 26% (F1-score) and 17.4% (accuracy).

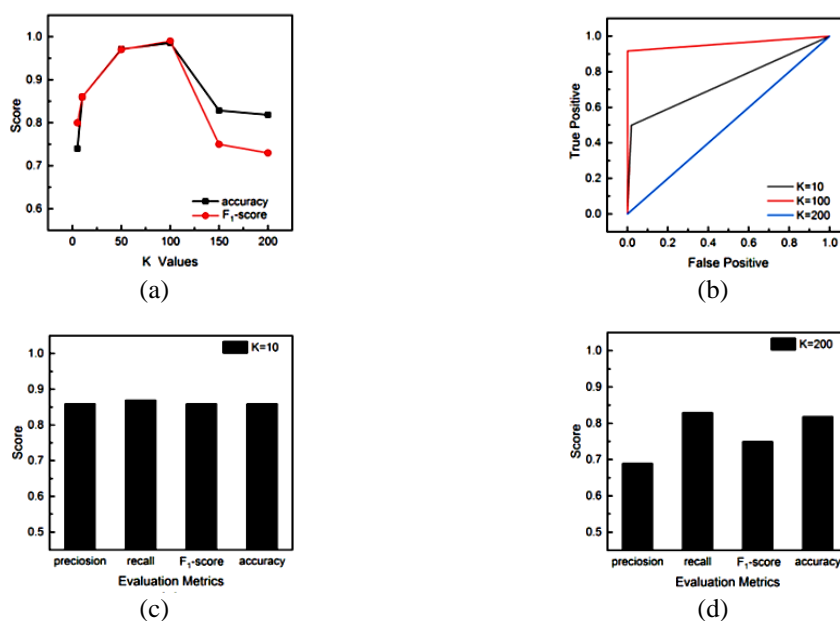


Figure 7. An investigation of the impact of  $K$  values on classification results; (a) for various  $K$  values, (b) ROC curves, (c) for  $K = 10$ , and (d) for  $K = 100$

Furthermore, the study further demonstrated that the characteristics of the top 100 aggregated pixels, as well as the bottom 100 aggregated pixels, are best able to represent the characteristics of the histopathology images. ROC curves and classification scores are used to highlight further the changes in classification outcomes for different  $K$  values. Alternatively, when  $K$  is large, cancerous tissue's image-level characteristics may include too many variables from normal tissue when  $K$  is small, whereas when  $K$  is small, cancerous tissue's characteristics may include too many variables from non-cancerous tissue.

In this study, the authors of the study recommended that a  $K$  value of 100 should be used in order to calculate the classification accuracy and the training costs for "liver cancer histopathology images with only global labels" in order to determine the classification accuracy of the images. According to the study that was published in this article, the proposed technique appears to be able to accurately identify liver histopathology images based on their characteristics when the  $K$  value is chosen correctly. This is based on the opinion that the proposed strategy could be successful in achieving good classification performance.

## 4.2. Classification performance

In this article, we present a method that can be used to distinguish between abnormal liver histology pictures and normal liver histology pictures. As a result of the authors' research, they propose a method to combine transfer learning with MIL. Figure 8(a) shows that our method produces good results on this binary classification task of 70 liver histopathology images when tested on a dataset of 70 liver histopathology pictures, as illustrated in our test dataset of 70 liver histopathology pictures. In this case, the precision score reached one, which means that the photos were correctly classified by the algorithm. Based on the validation dataset, it appears that the procedure performs well, with a recall of 0.99 and a precision of 0.99 on the validation dataset.

According to the authors, their system has been shown to be able to recover distinguishing characteristics from liver tissue images and to be capable of reliably categorizing them based on global labels alone. As can be seen from Figure 8(b), the ROC curves do not change significantly with the change in the liver histopathological image dataset, which indicates that while the method is capable of identifying "liver histopathological images" for which it has not been trained previously, it remains resilient in the face of changes in the liver histopathological images. Despite the fact that this approach is resilient, since it is capable of accurately detecting liver histopathology images that have never been trained on before. The confusion matrices in Figures 8(c) and 8(d) indicate that the technique efficiently finds discriminative qualities in the complex medical visualizations of liver cancer histology images, as shown in Figures 8(c) and 8(d).

During the implementation of our method, we tested it on the LiTS dataset [19], which consists of 131 CT images along with clinical annotations for each image. In this study, only 131 annotated CT images were taken into consideration. Moreover, for each patient, there are more than 150 slices included in the analysis. The images have been converted into JPEG format, and were obtained from a digital imaging and communications in medicine (DICOM) file of 630×630 pixels with a depth of 24 bits. The proposed model was found to be 98% accurate in the study in which the model was proposed.

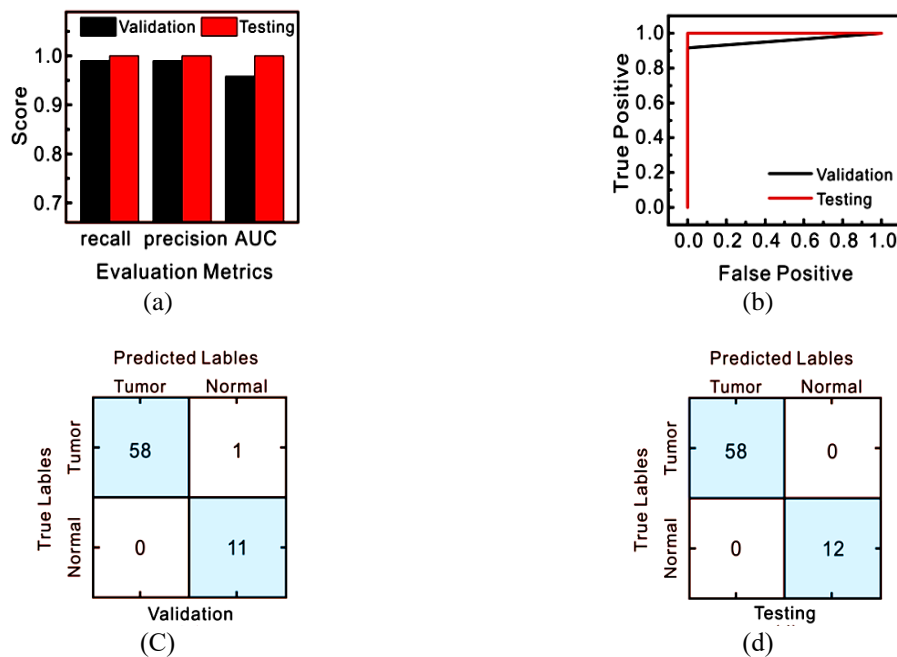


Figure 8. Classification performance; (a) recall, precision, and AUC values, (b) ROC curves, (c) the validation dataset's confusion matrix, and (d) the testing dataset's confusion matrix

## 4.3. Comparison with other methods

Figure 8(d) illustrates that the method presented here performs satisfactorily when it is only used to represent ground truth provided by TCGA. This study was performed to confirm the superiority of our method against methods that utilize patch-level features in combination with 2-norm and 3-norm averages to generate image-level features directly. On the basis of the procedure mentioned, we have derived the classification results shown in Figure 9.



In Figure 9(a), we show comparisons between the performances of these methods in terms of F1-scores, accuracy, and recall metrics that are used to measure classifier performance. Based on our experience, we believe our method is the most effective in terms of classification performance. The mean pooling method and the three-norm pooling method, however, have not achieved as good results as our method, which, with 98% of accuracy, 99% of F1-score and a recall value of 1, has achieved better results. In addition, the ROC analysis shows that our method meets or exceeds the performance of the other three methods shown in Figure 9(b) when employing only image-level labels. As part of the modeling process, the region indicating whether there are positive or negative instances of abnormal liver tissues and normal liver tissues is created to help build the best clinical features for abnormal liver tissues and normal liver tissues. Figure 8(d) shows that we can distinguish liver cancer histopathological images accurately with our method. Compared with this, in some cases it might be possible to identify liver cancer histopathological images correctly, but normal liver histopathological images are misjudged in some cases. There is evidence given by Figure 9(c) that a pooling method based on maximum data distinguishes liver cancer histopathological images, but does not correctly predict normal images, whereas a pooling method based on mean data and a pooling method based on three norms fails to do so. As shown in Figure 9(d) the result of a mean pooling method is that two histopathological images taken from normal liver tissue and two taken from cancerous liver tissue, respectively, would be normal images. There is a reduction in incorrect liver cancer image prediction when 3-norm pooling is used, but this is not true for incorrect liver tissue image prediction, as shown in Figure 9(e).

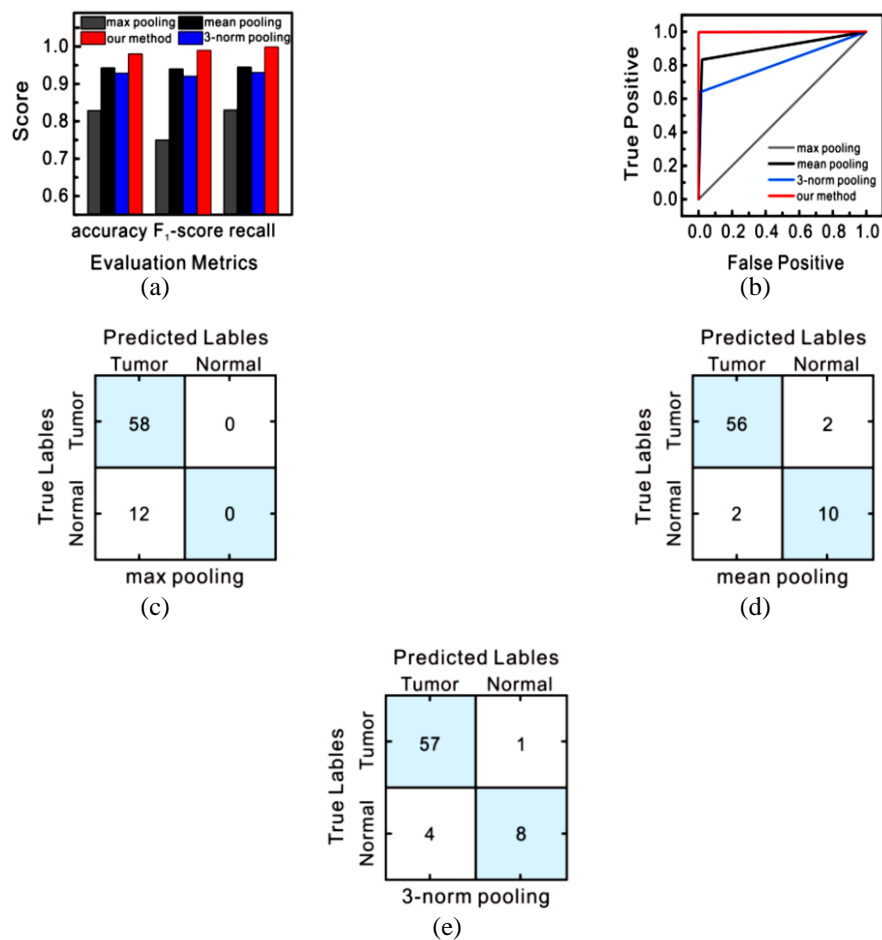


Figure 9. Performance comparison of different classification methods; (a) performance comparison, (b) ROC curves can be computed using a variety of methods, (c), (d), and (e) analysis of the confusion matrix for classification

In the case of max pooling, it will be possible to reserve only one patch-level pixel for the image-level pixel, rather than to reserve all the patch-level pixels for the image-level pixel in the case of max pooling. As a result of this process, it is not possible to fully reflect the characteristics of cancerous and non-cancerous

liver tissues. As we can see from the example, a large number of patches from histopathological images were maintained using a mean and three-norm pooling algorithm, along with a few patches from normal liver tissues, so we can see that there is a fair amount of feature in the final image that comes from normal liver tissues as well. This method uses transfer learning to extract representative characteristics of liver histopathological images into its algorithm to maximize patch information preservation so that top- $K$  and bottom- $K$  pixels can be employed to generate image-level features within the image. This method utilizes liver histopathological images to extract representative characteristics and preserve patch information to the maximum extent possible.

Several research papers were reviewed and analyzed in order to examine, test, and compare a selection of previously trained models against the proposed method in light of the review of the literature on the transfer of knowledge from previously trained models to the dataset used in this study, as shown in Table 1. Based on the review of several research papers on transfer of knowledge from previously trained models to different datasets, the proposed method was assessed, tested, and compared. In comparison with existing systems, the results of this study indicate that the proposed method has achieved good accuracy according to the results of the study.

Table 1. Performance comparison of our method with others

Author	Method	No. of CT images	Accuracy (%)
Shukla <i>et al.</i> [26]	Cascaded CNN	1421	94.21
Dong <i>et al.</i> [15]	HFCNN	NI	97.22
Ghoniem [27]	LeNet-5 + ABC	131	98.50
<b>Proposed</b>	<b>ResNet50 + CNN</b>	<b>462(TCGA)</b>	<b>99</b>
<b>Proposed</b>	<b>ResNet50 + CNN</b>	<b>131(LiTS)</b>	<b>98</b>

## 5. CONCLUSION

In this paper, we present a method for automatically recognizing liver tumors from histopathology images using mixed transfer learning and MIL. In this method, we emphasize the importance of reducing the reliance on detailed labeling and training datasets. There is a lot of potential for further development of this technology, which would allow for personalized treatment and increase its relevance to different types of cancer. Firstly, the paper presents a method that uses a combination of minimum likelihood and mixed transfer learning to classify liver cancer histopathological images employing only global labels and mixed transfer learning practices. This method has been demonstrated to be capable of accurately classifying liver histopathological images based on the experimental results in order to differentiate between cancerous and non-cancerous liver images. There are many advantages associated with this approach, such as reducing the need for extensive histopathological images to a minimum, resulting in detailed annotated labels that are annotated by pathologists who have extensive experience in this field. In addition to allowing the classification of histopathological images for the subtypes of liver cancer and other types of cancer, the method has the potential to support the development of personalized treatments for individuals with liver cancer.





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