Analysis on segmentation and biomarker-based approaches for liver cancer detection: A survey

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Abstract

Liver cancer is the major reason for death in this entire world. Manual detection of cancer tissue is found time consuming and difficult. Therefore, the development of an automatic detection approach with high accuracy for liver cancer is considered as the main aim of this work. The image processing approach can use the CAD for the classification of liver cancer in order to assist the physician in the decision-making process. An automated approach to effective classification of the liver tumour using effective features is conveyed in terms of the CAD system. Traditionally, radiologists delineate the liver and liver lesion on a slice-by-slice basis, which is time consuming and susceptible to inter- and intra-rater variations. Automatic methods for the segmentation of liver and liver tumours are, thus, highly demanded in clinical practice. A systematic review is being carried out to detect reported liver cancer from 2013 to 2020. Finally, a more precise technical direction is provided for all researchers in this review. Research gaps for earlier detection and its potential future aspects are also discussed.

1 | INTRODUCTION

In economically developed countries, the main source of death is a tumour. All over the world, the death rate is increasing because of the development of population, especially in less created nations, about 82% of the total population lives [1,2]. Around 90% of tumour-causing death is brought about by metastasis. This is a procedure wherein the primary tumour cell masses move to the far-off site and get multiplied to form the second stage of the tumour. It includes the events wherein primary tumour cells attack the encompassing tissues and also move into the microvascular blood cells as well as lymph. Then, cells go to small-scale vessels of removed tissues via circulation system, further exit from the circulatory system, and persist in the microenvironment of tissues about cell expansion and development of the subordinate stage of tumour [3,4]. Over the previous decades, miRNA investigates mainly on the tumour. Also, numerous examinations have exhibited the significance of miRNAs in tumour biology to encourage angiogenesis, invasion, attack, tumour evolution, and then immune evasion [5]. The advancement of various high-throughput miRNA profiling advances has permitted the portrayal of the miRNA articulation profile for few malignancies, including constant lymphocytic leukaemia, lung malignancy, breast tumour, thyroid papillary carcinoma, pancreatic tumours, glioblastoma, gastric malignancy, prostate disease, and hepatocellular carcinoma (HCC) [6,7].

The sixth most diagnosed disease is liver cancer [8]. It does not simply influence the liver; furthermore, it also damages the processing of the whole body. Liver disease is frequently brought about due to hepatitis B or C, so it is critical to see how to prevent these sorts of hepatitis when thinking about liver malignancy counteractive action [9,10]. The most well-known and powerful imaging procedure for identifying liver tumours is computed tomography (CT) [11,16]. It gives pictures of the liver with the help of successive multiphase scans after the infusion of differentiation media [12,13]. Frequent damage caused by the liver in bile synthesis and detoxification is mainly due to its large regenerative potential [14]. The approaches, like image processing, as well as artificial intelligence, are largely utilised to classify the liver tumour [15].

This enhances the identification of abnormal liver cells by increasing the lesion-to-liver contrast, also facilitating the lesion characterization in some situations [17]. An effective
interventional radiological therapy is reported as the tumour growth, along with the transarterial chemoembolization due to an increase in patient survival [18]. The various ways of liver tumour image logical diagnosis include ultrasonic scan, magnetic resonance imaging (MRI), CT, and then angiography. Generally, CT [19] image is preferred by the doctors in early diagnosis of the liver tumour due to its low damage, the ability to reflect the pathological position, as well as high resolution accurately. The procedures such as image guided surgery (IGS), segmentation, and organ imagining also play a key role in medical image analysis. In abdominal CT images, it is challenging to perform the segmentation process due to the overlap of a variety of organs that lie within uniform intensity ranges [11].

A biomarker is a measurable biological characteristic that indicates the presence of some disease state [20]. Tumour biomarkers can predict disease recurrence in liver transplant recipients [21]. Tools and technologies of genomic biomarkers estimate the probability of an early positive biopsy, which minimise the number of unnecessary repeat biopsies, sub-stratify risk tumours, classify the disease extent, as well as monitor the clinical response [22]. This comparative study is performed on both the segmentation and biomarker-based liver cancer detection to analyse the capability of both the approaches. Therefore, it is necessary to identify liver cancer with suitable technique at the primary stage. To achieve that, several researchers are now working on both segmentation and biomarker fields to identify the suitable technique for liver cancer detection. In this comparative study, some of the techniques that have developed for liver cancer detection are reviewed and discussed. This comparative study provides valuable information to researchers who are seeking knowledge about biomarker- and segmentation-based liver cancer detection approaches.

The basic introduction for liver cancer detection and its stages is explained in Section 2. Then, the basic details about segmentation and the steps involved in segmentation-based liver cancer detection are explained in Section 3. Next, in Section 4, the basic information about the biomarker and genomic biomarkers are explained. Next, the literature review for segmentation- and biomarker-based liver cancer detection is explained in Section 5. Finally, the conclusion and future consideration are discussed in Section 6.

2 LIVER CANCER DETECTION

The liver is the principal organ in the abdomen, which is mainly affected by various kinds of tumours. The first type is the primary tumour, and it forms within the liver. The other names are hepatoma or else HCC. The next type is secondary tumour; it originates in other organs and then spreads to the liver [30]. It is necessary to examine the extent of disease to plan suitable therapies. Specifically, the patient’s survival rate can be enriched using earlier diagnosis and treatment, which reduces the cost of treatment [31]. Tumour patients can be treated by utilizing a liquid biopsy test that hints at the doctors with an essential range of information needed for treatment. This is a substitute for surgical biopsies, performed by means of a simple blood sample. The application of liquid biopsy in detecting tumours has been explored recently, which analyses the circulating tumour cells as well as other nucleic acids in blood [32]. The liver tumour includes four stages, namely, benign, epithelial, malignant, and non-epithelial. These four classifications are shown in Figure 1.

The entire algorithm for this liver cancer detection process is shown in Figure 2. Here, initially, the image obtained by CT is classified to detect whether it is normal or abnormal. If the obtained image is normal, then the individual does not require any treatment. Or else, if an abnormal condition is identified in the image, then it is essential to provide treatment by the chemotherapeutic drug. This treatment procedure is continued till the end.

Rajagopal and Subbiah presented a novel automatic liver tumour segmentation approach using CT scans to achieve accurate results. The suggested approach does not require any manual interface as well as it detect various kinds of liver tumours. A segmentation algorithm regarding feature extraction, in addition to support vector machine (SVM), was proposed to identify tumour [24]. Sun et al. introduced an approach named fully convolutional network (FCN) for tumour segmentation in liver. Also, to segment the tumour from multi-phase contrast-enhanced CT images, a multi-channel FCN was designed [15]. Massopiot and Casciaro developed a graph-cut method using adaptive threshold initialization for segmenting complex liver geometries [35]. Treatments such as radiotherapy, in addition to liver ablations, need accurate knowledge of liver structure that consists of lesion localization, liver surface, as well as blood vessel topography. Local treatment planning is the first important step to obtain accurate liver surface [25].

Ben-Cohen et al. introduced two approaches: a global context with an FCN and the classification approach based on superpixel sparse for local patch level analysis. This work mainly focuses on detecting metastatic growth in CT [26]. Chen et al. proposed a diagnostic approach named contrast-enhanced ultrasound imaging (CEUS)-based classification of liver disease [27].

A watershed Gaussian-based deep learning technique was introduced by Das et al. for describing liver tumour lesions in CT images. Two hundred fifty-five images were processed to create a model. In the first phase, the liver was separated utilizing the watershed segmentation; then, lesion affected by tumour was segmented with the gaussian mixture model (GMM) algorithm. After that, the extraction of texture features is performed. Then, the extracted features are fed to a classifier named deep neural network (DNN) for automated classification of liver cancers such as hepatocellular, metastatic carcinoma also haemangioma [28]. Evers et al. [29] developed a technique named diffuse reflectance spectroscopy (DRS) that utilises an optical fingerprint to differentiate the normal tissue from tumour-affected tissue. In order to gather DRS spectra among 500–600 nm, a miniaturised optical needle was developed. The number of measurements was completed, as well as the outcomes of DRS were also compared. The degree of hepatic steatosis by means of high accuracy was projected using the DRS method.
Stage I
Only one tumor in the liver

Stage II
Only one tumor which has grown into blood vessels, or multiple tumors, none more than 5cm across

Stage III
Multiple tumors, at least one more than 5cm or growing into the portal vein, hepatic vein, a nearby organ other than the gall-bladder, or the outer covering of the liver

Stage IV
Cancer that has spread to nearby lymph nodes or other parts of the body

FIGURE 1 Liver cancer stages

FIGURE 2 Flowchart for Liver cancer detection
3  |  LIVER CANCER DETECTION USING SEGMENTATION

The prominent steps that are applied to identify liver cancer from medical images are image enhancement, segmentation, and feature extraction. These three processes are performed in medical images to identify liver cancer. This image enhancement process is also referred to as a pre-processing step. The first stage is to process the input image for further processing. In biological research, as well as diagnosing the disease, a high-quality MRI medical imaging method is utilised to represent the organ structure of humans in a more defined manner. By classifying the image exactly, the outcomes of the MRI image are improved. Image segmentation is the second stage to identify the tumour cells.

3.1  |  Image enhancement

The process of image enhancement is similar to image processing. The reason for the procedure of the picture upgrade is to improve the picture quality for the human eye. This process enhances the quality of the image with fewer errors. Spatial and frequency-domain techniques are the two categories of image enhancement. Image pixel direct manipulation is called spatial domain, whereas the use of wavelet or else Fourier transform defines the frequency domain. Also, it characterises the rate at which pixel outcomes are varying in the spatial domain. It cannot be resolved that what kind of strategy is useful for picture upgrade [30,32].

3.2  |  Image segmentation

The method of dividing an image into several subdivisions is termed as Image segmentation, mainly suitable for performing the number of tasks in image processing. In medical imaging, segmentation is represented as an automatic 2D/3D image boundary detection. The automatic detection of boundaries has applications in cell counting, organ measurement, tumour detection, visualization etc. Other approaches such as image recognition and description highly depend on image segmentation. The chief goal of segmentation is image simplification, which also makes it more beneficial for the analysis purpose.

3.3  |  Feature extraction

The most significant procedure in image processing is feature extraction. One of the most suitable techniques preferred for extracting features is termed as a wavelet transform. It also has the property of examining the image using varying resolution unit, which also consists of multi-resolution analytic property. The wavelet transform outperforms Fourier transform in addition to short-time Fourier transform because it preserves both times and frequency [30]. Curvelet transform was suggested by S.S. Kumar and Dr. Moni to detect a tumour in the liver. Initially, the liver was segmented using an adaptive threshold decision in addition to morphological processing; then, a neural network was trained to recognise tumour type [49]. A deep convolutional neural network (CNN) process that extracts tumour cells automatically from CT images was developed by Li et al. [50]. Some sample outcomes of segmentation are mentioned in Figure 3. Green contours represent the manual segmentations created by experts; however, red contour indicates segmentation. In the 3D-IRCADb dataset, FCN segmentation outcomes are shown in Figure 3(a) and (b), and the outcomes of the JDRD-H dataset are mentioned in Figure 3(c) and (d) [15].

4  |  LIVER CANCER DETECTION USING BIOMARKER

4.1  |  Biomarker

Biomarkers are normally developed by cancer biology. A large number of ways are available to characterise cancer, but here, we mainly focus on cancer biology due to the logical concept developed by this cancer biology. It mainly focuses on the biomarkers at the cellular, tissue, and molecular level. The development of cancer may disrupt the normal functioning of tissues, organs, and cells. This may occur mainly due to some genomic changes amplifications and deletions, mutations, epigenetic modulation of gene expression, and genome rearrangements. In clinical cancer, the clonal and cellular heterogeneity, as well as unregulated cellular proliferation, may characterise the final outcome of this chaotic process. Therefore, at the molecular target sites, an effective therapeutic intervention is found transient and
subsequently trailed by therapy resistance [53]. The genetic changes introduce the hallmarks. Cancer progression is identified as an evolutionary process because the clonal selection of the altered cells evade the immune surveillance and also thrive in stressful condition due to the disruption produced in an ordinary cellular function [44]. The cells that perform the clonal selection process contain five features: metabolic stress, DNA damage, mitotic stress, oxidative stress, and pro-apoptotic stress. These features are considered as stress phenotypes of cancer. The molecular events and the features that precede them are normally recognised as the sources for cancer biomarkers, and then, they are taken as a target for therapeutic intervention.

Even though a large number of genetic variants are taken into consideration, but only 23,000 genes encoded with human genome are considered as a base by more than 1 million potential protein–protein interactions. In contrast, some of them may have neoplasia characteristics. Advancement in tissue pathology (particularly the pathology imaging), genomics, cellular, and molecular biology provides tools to detect and evaluate the cancer progression biomarkers. Currently emerged drug development approaches apply predictive biomarkers. The biomarkers are normally applied to select the patients, so these biomarkers are applied in clinical trials while developing the new drugs. These clinical trials are developed to identify the effect of drug over the patients instead of identifying it for biomarkers. By taking the presence or absence of the biomarker into account, the decisive trials are frequently stratified (for data analysis or patient randomization). The biological knowledge obtained by this innovative drug indicates that its effectiveness may strongly correlate with the available biomarker. Due to this correlation, the patients who show positive results for biomarkers are highly enriched with Phase II proof-of-concept studies (and perhaps with registration studies). This enriching process is identified as an effective way for drug evaluation. The personalised medicine is advanced by employing the biomarker; meanwhile, the changes that happen in biomarkers are evaluated by the approved drugs.

The biomarker is also characterised by the following [51]:

- **Feasibility**: Biomarker shows feasible in detection and measurement, but based on the sample collection type, methods, or processing procedure, it does not exhibit much variability during its identification process.
- **Non-invasiveness**: Without involving the invasive procedures like muscle biopsies, it supervises the disease over time and also at various time points by applying the scanning techniques (e.g. PET or MRI) or by allowing the access and measurement in body fluids (urine/blood).
- **Effectiveness in cost and time**: During each clinical trial, cost and time need to be maintained as it is measured from various time points, and also, it observes the entire disease or treatment course.

The biomarkers that satisfy these features may attain improvements in clinical trials, which is identified as the most promising objective of this biomarker. According to the European Medicine Agency (EMA), it allows them to perform the process in a small, particularly selected, cohort, and also within a short time period. An ultimate objective of this is to provide “the right drug to the right patients at the right time”. The process flow for cancer identification using biomarker is illustrated in Figure 4.

5 | REVIEW ON METHODOLOGIES OF LIVER CANCER DETECTION

5.1 | Segmentation-based detection approaches

This paper makes use of distinct approaches, namely, the watershed algorithm and edge detection; then, region merging is accomplished to segment liver tumours from CT images effectively. Among the suggested approaches, the watershed algorithms works better in segmenting liver tumour, also avoiding over-segmentation process as well as achieving contour of lesion section accurately [25]. A new technique was introduced to segment the liver automatically mainly for calculating the volume in sequential CT images. The morphological filter utilises region-labelling, and clustering, to examine the liver contour with fixed search range. A labelling-based search algorithm is utilised to deform liver contour [34].

A technique named complex geometries was proposed for segmenting the liver automatically. The adaptive threshold was initialised by performing the graph-cut method. Automatic liver segmentation was established by the graph-cut method [35]. A model named active contour is utilised in tumour segmentation as of abdominal CT images. Outside the region of tumour, boundary is drawn manually by operators. In radiology, the calculation of tumour volume is an important task [36]. This article presents a review of the competition of 3D segmentation in the clinic. The chief goal of this contest compares various algorithm presentations for segmenting liver tumour from CT images. Data are taken from 30 liver tumours like haemangioma, HCC, and metastasis [37]. Automatic hepatic tumour segmentation of a CT image is performed by means of the optimal statistical threshold. Techniques such as multi-modal threshold, histogram transformation, binary morphological filtering, and maximum posteriori decision are utilised to segment the liver structure [38]. The manual segmentation process consumes more time, so this automatic tumour detection and segmentation process acquire more significance. In [40], the two

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**FIGURE 4** Cancer identification using biomarker approach
consecutive fully connected CNNs are used. Among these two, one is applied for liver segmentation, and the subsequent one is to segment the actual tumour that is present within the liver [41].

For liver segmentation, CT images permit the 3D structure extraction of liver tissues, where the comparative location is noticed for the treatment of interventional surgery or else radiation therapy. Here, the prevailing CNN approach is applied in the adequate receptive field, which successfully enhances the process of segmenting such a large organ from the neighbouring organs in CT images. Still, there exist some demerits, so they highly depend on post- or pre-processing techniques to enhance the final segmentation process. The liver segmentation process in CT images is improved by implementing the effects of dilated convolutional networks [39]. Recently, the introduction of deep learning in image segmentation has improved the segmentation result. The 2D segmentation design based on the Feature-fusion Encoder–Decoder Network is introduced to achieve high performance but with minimum complexity. It is also developed to overcome the issues that are obtained while segmenting the liver lesion from CT images [42]. The different types of segmentation approaches are discussed in Table 1.

5.1.1 Different types of segmentation approach

A large number of studies are performed on this segmentation process, and various algorithms are developed for the segmentation process based on the semi-automatic and fully automatic degree. The methods that are included in the segmentation approach are listed as follows:

(i) region-based/contour-based segmentation methods;
(ii) thresholding-based technique;
(iii) model-based approach;
(iv) level-based approach;
(v) graph cut.

Region-based segmentation approach

This segmentation approach highly depends on the intensity levels of adjacent pixels. However, the geometrical or statistical active shape is included in the contour-based segmentation process. These two approaches have separate merits and demerits over computational cost, performance, and applicability. This region-based approach achieves better results from the high-contrast images. This segmentation approach groups the pixels that have similar characteristics within the distinct regions. The two techniques included in this segmentation process are region splitting and region growing. Initially, a very small group of the segmentation process is estimated in the region-growing approach. An iterative process is applied in this region-growing process to recover the surface of interest. The homogeneous neighbours are then included in this region-based segmentation by expanding the seed region; however, this expansion process is continued till attaining the entire segmented parts. In [44], the liver segmentation process is performed by implementing an improved $k$-means clustering algorithm. The cyst area found in the liver is segmented accurately by applying the morphological opening for the outcome of the $k$-means clustering algorithm. Another approach is developed in [51] for segmenting the liver tumour by applying the fuzzy c-means (FCM) clustering algorithm. But, this method is found ineffective for clusters with unequal shape or volume; also, it is found ineffective for clusters that have noise or outlying points. This defect is overcome by developing alternative FCM algorithm.

Threshold-based approach

The foreground objects are separated from the background by applying adaptive thresholding, local adaptive thresholding, and global thresholding with respect to the differences that are found between the pixel intensities of the liver regions. The

### Table 1 Types of the segmentation approach

| Process                  | Types       | Contribution                                                                 |
|--------------------------|-------------|------------------------------------------------------------------------------|
|                           | Region-based| • Region-based segmentation approach highly depends on the intensity levels of adjacent pixels. |
|                           |            | • This segmentation approach groups the pixels that have similar characteristics within the distinct regions. |
|                           | Threshold-based| • The foreground objects are separated from the background by applying adaptive thresholding, local adaptive thresholding, and global thresholding with respect to the difference that is found between the pixel intensities of the liver regions. |
|                           |            | • This approach is fast, simple, and computationally less intensive, so it provides better outcomes for CT liver images. |
| Segmentation              | Model-based| • Initially, the global shape and pose properties were estimated on the basis of scanned low dimensional area in training set. Using this, the algorithm of template matching is performed for recovering the local deformations. |
| approach                  | Level-based| • The muscles present in the liver extracted carefully by Level-set-based approaches to perform accurate liver segmentation processes. |
|                           | Graph cut-based| • A novel technique is developed to perform the liver segmentation. Here, the contrast-enhanced MRI with multiphase is applied with optimised global tree-metrics in terms of graph-cut approach. |
|                           |            | • In the final step, the tree-pruning technique is applied to minimise the available amount of labels in the liver segmentation process. |
fixed threshold is employed by global thresholding for all image pixels, so this input image is employed only if its intensity histogram is clearly obtained without any peaks with respect to the desired background and object. Alternatively, a unique threshold is selected by local adaptive thresholding in terms of intensity values for all pixels. An altering lighting condition that is obtained in an image is accommodated by adaptive thresholding. For each pixel, the adaptive thresholding is applied to detect the local threshold for analysing the intensity values found in the local neighbourhood [43].

Model-based approach
Saddi et al. 2007 [61] developed a two-stage algorithm to perform the liver segmentation technique. In this technique, initially, the global shape and pose properties were estimated on the basis of scanned low-dimensional area in the training set. Using this, the algorithm of template matching is performed for recovering the local deformations. Schmidt et al. [46] introduced a cognitive network technology in the rule-based approach to perform the liver segmentation process. The pixel classification attained by a semantic knowledge-based technique is employed here. Finally, a mean overlap error of about 16% is attained by this liver segmentation approach. An algorithm of active contours and multiple seed point k-means clustering methods are integrated to develop another technique for liver segmentation. The segmentation process based on modified k-means is united with the localised contouring algorithm; this united concept is identified as a novelty in this algorithm. Five distinctive regions identified from the input CT images are highly required for this k-means segmentation process. Then, a novel algorithm for localised contouring is developed in terms of local region thresholding [46].

Level-based method
The muscles present in the liver are extracted carefully by level-set-based approaches to accurately perform liver segmentation process. In [47], the statistical pixel-classification-based level set algorithm is developed for lesions segmentation. In [52], the two techniques (i.e. adaptive curvature and multi-resolution 3D level set) are coupled to classify the pixels into background and tumour. After accomplishing the level set smoothing and minimum-entropy-based region-growing methods, a semiautomatic approach is developed in [45] by employing an initial watershed segmentation algorithm.

Graph-cut-based approach
In [48], a novel technique is developed to perform the liver segmentation. Here, the contrast-enhanced MRI having multiphase is applied with the global optimal tree-metrics-based graph cut algorithm. Initially, the feature set is extracted from these MRI data. The spatial–temporal information that is present within the MRI intensity images is revealed by applying the colour space mapping over it. For the contrast-enhanced multiphase MRI data, an effective tree-metrics graph cut algorithm is applied by employing an unsupervised architecture to attain the optimal global labelling. In the final step, the tree-pruning technique is applied to minimise the available amount of labels in the liver segmentation process. Three parameters are provided as an input for this algorithm: 1) labels tree; 2) a multiphase contrast-enhanced MRI liver image; and 3) a smoothness parameter \( \lambda \geq 0 \). On the basis of mined dynamic features, a labels tree is developed through agglomerative clustering.

5.2 | Liver cancer detection using genomic biomarker

5.2.1 | Genomic biomarkers

Based on the definition of EMA/US Food and Drug Administration, both RNA and DNA determinants like allele variations or polymorphisms are included in genomic biomarkers. In contrast, this determinant may highly depend on therapeutic response or disease progression, disease susceptibility. Recently, high-throughput technologies like next-generation sequencing (NGS) and microarray platforms are developed. These technologies facilitate the studies regarding the variability of the human genome, whereas it furthermore enhances the likelihood of biomarker discovery. While comparing to the standard Sanger sequencing technology, the genomic nucleotide fluctuations found in numerous samples can be simultaneously identified by the novel NGS platform at reduced cost and time. In both healthy and affected subjects, the gene configuration and RNA/DNA levels are examined quantitatively along with microarray technologies during the same and diverse time points. Recently, the MicroRNAs (miRNAs) are identified as a good biomarker for analysing the disease severity, so later, various researchers largely focused on this biomarker.

Mizuno and his colleagues [60] examine the muscular dystrophy models of serum animals and identify the advanced stages of muscle-specific miRNAs (myomir) [50]. The neuromuscular disorders having severe phenotypes contain a higher level of myomir; this severity represents the disease severity biomarkers as prime candidates. Furthermore, Eisenberg and his collaborators [62] performed a comparison among diseased and normal skeletal muscles, which shows that the signature of specific miRNA can be distinguished among the diseased and normal muscles, and also between the various types of neuromuscular disorders. Epigenomic modifications are also identified as a genomic biomarker, which plays a major role as both prognostic and diagnostic biomarkers. Recently, the clinical results of Friedreich’s ataxia (FRDA, OMIM 229300) correlate the DNA methylation. Early drivers of tumour progression and tumour genesis are attained from the mutations in both protein coding and non-coding portions. Data testing is performed to identify the meaningful association among phenotypes. During such a process, the variants become too sparse, as the mutation is found at adaptable positions across the individuals. In order to avoid this, a novel gene-to-protein-to-disease (GPD) is developed. This GPD-segmentation-based mapping process accumulates the modified information by applying novel sequence units. It is identified that the modified frequencies of each sequence unit are highly reproducible among a pair of huge cancer cohorts [43].
5.2.2 | Discovering predictive biomarkers

Before collecting the tumour tissue, it is necessary to identify which measurement will accurately detect how the patient’s will respond to treatment. The gene-expression signatures have the same value as that of prognostic biomarkers, but they are found less convincing because they do not predict the patient’s response to a particular treatment. The number of samples that are available for formal hypothesis evaluation is too small because more recent treatment studies associated with tissue collection are found incomplete. Earlier review suggests that the tissues that are produced during diagnosis are completely analysed by the prognostic biomarker studies. An alternative solution for the signatures of gene expression in preclinical (like animal and cell line models) models is to search the candidate predictive gene-expression signatures. Alternatively, the tumour DNA genotyping is identified as a valuable one for predicting the response of the patient to treatment, but its broader application in this clinical field remains vague. The process of predicting the response of each patient to treatment is identified as the difficult task during secondary mutations, which is also highly revealed by these studies.

The DNA copy-number valuation is incorporated by predictive biomarkers along with mutation detection. The resistance for furthermore protein kinase inhibitors is normally related to the secondary mutations while encoding the genes of drug target. Due to these reasons, this mutation is identified as a major explanation for treatment failure. Initially, only a minute quantity of tumour cells contains the drug-resistant alleles. So, highly sensitive techniques like single-molecule sequencing for the detection process are required. The mutation subjected in additional genes like PTEN or RAS diminishes the sensitivity that is present in the inhibitors of the mutated drug target (like glioblastoma, multiforme, and lung cancer). Therefore, these extra variables are incorporated by the predictive biomarker. Temporarily, most of the hypothesis-driven techniques like genotyping patients are applied for well-known cancer-associated mutations using the platform that can straightforwardly expand to aggregate the discoveries. The targets are obstructed by most of the anticancer agents in a particular molecular pathway so that pathway-specific biomarkers can be viewed as an additional option in the future.

Till now, only a few studies have been performed with few antibodies in the pathway activation biomarker. More global techniques, those highly depend on mass spectrometry, are applied as an initial screening step for tumour identification. This is very much suitable to accomplish the focused sequencing initially; after that, it will detect the causative genetic lesion. Based on the direct assessment that is performed on pathway substrates, these approaches measure the pathway activation. A large number of indirect approaches may apply the gene-expression signatures, whereas its pathway activation related to the particular gene-expression signature is exposed for a cell line that is constructed to depict particular oncogenes.

5.2.3 | DNA damage biomarkers (DNA-DB) as predictors of cancer risk

The cancer development may take numerous years to decades, so it is practically not possible to carry out an approaching epidemiological study for such a long duration. So, now experiments are going on in these biomarkers to determine whether they can able to predict the cancer risk at a short duration. The susceptibility factors highly influence the biomarkers of clinical disease, exposure, and effect by including polymorphism. Because it can alter the performance of carcinogen metabolism, apoptotic pathway genes, and relevant DNA repair, the activity of the gene is also altered by these dietary factors. Multiple mutations are included in this cancer, so it is difficult to identify whether the generic biomarker that producing hyper-mutation is as essential as some common events in cancer cells like p53 inactivation or apoptosis. The major demerit obtained in DNA-DBs during human studies is accessible tissue relevance; here, the damage found in DNA is identified (e.g. lymphocytes, exfoliated epithelial cells, and erythrocytes) for studied cancer (e.g. colon, prostate, and breast). Finally, the measurements are also performed for similar issues. It requires more time and numerous laboratory’s determinations to study the estimation of a single DNA-DB for cancer prediction.

Recently, the validation process has been reviewed [41], whereas it contains three primary stages: (a) developing standardised protocols by taking expression time, sample acquisition, and sample storage into account; (b) determining an essential lifestyle, demography, and methodology; furthermore, it also determines the genetic variables as they highly influence the measured index; and (c) testing of prospective and control of the biomarkers while predicting the cancer risk most particularly for specific cancer. In all stages, the cytogenetic biomarker that is outlined formerly is classical metaphase, which is applied to measure the CA (i.e. chromosome split and rearrange) in human lymphocytes [42]. This indicates that maximised chromosome damage also introduces cancer in human beings.

5.2.4 | Review on genomic-biomarker-based liver cancer detection

Advanced genomic, proteomic, and metabolomic biomarkers are considered as a variety of novel biomarkers for HCC. Some additional biomarkers are being developed for diagnosing HCC, predicting the patient condition, and treatment results; furthermore, the usage of targeted therapies is being individualised. However, the recent application of HCC biomarkers is screening, which is used at the early stage, intending to reduce HCC mortality. Extremely upregulated lncRNA in liver cancer (HULC) had been involved in regulating the proliferation of hepatoma cells. In [54], the expression of HULC in HCC tumours is shown, which is found significantly higher than in normal liver tissues. For patients with higher Edmondson grades or having Hepatitis B-virus (HBV)+ status, higher HULC detection levels are identified in plasma.
The serum/plasma miRNAs will discriminate against controls against HCC patients. However, Wen et al. [55] developed a method to recognise and test HCC-associated miRNAs coming from the liver as early biomarkers for HCC detection. Nucleoside analogue therapy in patients with chronic Hepatitis B (CHB) will effectively inhibit HBV replication and thereby decrease the risk of developing HCCs. However, to treat patients with adequate suppression of HBV DNA replication, the risk of HCC is considerably larger than inactive CHB patients, without considering about the existence of standard liver cirrhosis, which represents a predisposing, long-lasting, strong HBV effects. Explicit oncogenic impacts of HBV incorporate infiltration into the host genome prompting cancellation, transactivation, translocation, combination transcript creation, and summed up genomic precariously, just as viral transcript pleiotropical impacts (HBx and HBsAg). Examination of these viral factors in dynamic reconnaissance may allow early discovery of high-chance patients, and their fuse into a sub-atomic arrangement of HCC subtypes may help set up new restorative methodologies [56]. Molecular markers [57] are not used to identify patients or to assess their prognosis and treatment. Patients with signs of HCC and/or vascular invasion and/or extra-hepatic cancer are known to have advanced-stage cancer and may benefit from treatment with a sorafenib kinase inhibitor. In order to check the assumption that genome-wide dysregulation provided by circulating miRNAs differentiates HCC cases from controls, i.e. a two-phase case control [58] (20 pairs—discovery set, 49 pairs—validation set) analysis was performed. alpha-fetoprotein (AFP) [59] is the most commonly applied serum biomarker worldwide for detecting HCC. Identify the imaging and molecular marker techniques that are capable of identifying HCC patients in earlier stages and better predicting their survival period, and treatment responses were reviewed in the above topics. The performance comparison for different classifiers using CT and MRI datasets [24, 26, 48] is tabulated in Table 2. The classifiers that are considered here for comparison are multi-layer perceptron (MLP), SVM, and random forest (RF). Among these three classifiers, the MLP approach has shown better performance in liver cancer detection. The time complexity shown by this MLP classifier is found less than that of other two classifiers.

The performance comparison for some basic parameters like specificity, sensitivity, accuracy, area under curve (AUC), positive predictive value (PPV), and negative predictive value (NPV) for some blood biomarkers are enumerated in Table 3. From these two tables, it is finalised that the detection result provided by biomarkers is found better than those provided by CT- and MRI-based detection techniques. Due to these benefits, now, the biomarker-based cancer detection is highly considered by various physicians.

### 6 CONCLUSION

The detection process for liver cancer is receiving a huge demand. Therefore, in this work, various segmentation approaches and their performances are reviewed along

| TABLE 2 | Performance metrics of different classifiers using CT, MRI, and combined dataset for liver cancer detection |
|---------|---------------------------------------------------------------|
| Metrics | Methods  | CT         | MRI        |
|---------|----------|------------|------------|
| Sensitivity | MLP  | 0.974      | 0.959      |
|          | SVM     | 0.969      | 0.958      |
|          | RF      | 0.968      | 0.944      |
| Precision | MLP    | 0.98       | 0.959      |
|          | SVM    | 0.969      | 0.958      |
|          | RF    | 0.97       | 0.946      |
| Kappa statistics | MLP   | 0.9693     | 0.9507     |
|          | SVM    | 0.9627     | 0.9493     |
|          | RF    | 0.937      | 0.9333     |
| AUC     | MLP    | 0.995      | 0.979      |
|          | SVM    | 0.998      | 0.996      |
|          | RF    | 0.997      | 0.986      |
| Time (Sec) | MLP   | 0.27       | 0.42       |
|          | SVM    | 0.12       | 0.31       |
|          | RF    | 0.11       | 0.11       |
| F-measure | MLP   | 0.975      | 0.959      |
|          | SVM    | 0.969      | 0.958      |
|          | RF    | 0.968      | 0.944      |
| RMSE    | MLP    | 0.3113     | 0.1152     |
|          | SVM    | 0.0874     | 0.1083     |
|          | RF    | 0.1542     | 0.3125     |
| MAE     | MLP    | 0.2228     | 0.0154     |
|          | SVM    | 0.0176     | 0.0276     |
|          | RF    | 0.0302     | 0.2236     |

| TABLE 3 | Performance comparison of blood biomarkers for liver cancer detection |
|---------|---------------------------------------------------------------|
|            | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV | NPV | AUC |
| CEUS [27]  | 85               | 91              | 86.36        | –   | –   | –   |
| AFP [59]   | 85.6             | 93.3            | 65.5         | –   | –   | 0.754
| GP-3       | 55.1             | 97              | 89.5         | 57.1| 51  | 0.850
| DCP        | 72.7             | 90              | –            | –   | –   | 0.6798
| GP-3+AFP   | 75.5             | 83.3            | –            | –   | –   | 0.898
| DCP+AFP    | 87               | 69              | –            | –   | –   | 0.7586
| miR-21     | 61.1             | 83.3            | 80.17        | 75  | –   | 0.865
| miR-122    | 87.5             | 97-97.5         | –            | –   | –   | 0.785
| miR-224    | 87.5             | 97-97.5         | –            | –   | –   | 0.880
| miR-122+AFP| 97.5             | 100             | –            | –   | –   | 0.849
| miR-15b    | 98.3             | 15.3            | 56.03        | 52.83| 90 | 0.485
| miR-130b   | 87.7             | 81.4            | 84.48        | 81.97| 87.27 | 0.913
| miR-4835p  | 75.5             | 89.8            | –            | –   | –   | –   |
with some essential details regarding the genomic biomarker approach. The segmentation process enhances the cancer detection process. In recent days, various literary works have focused on biomarkers to improve liver cancer detection. To apply the DNA-DBs in the future, the perfect integration of both prevailing techniques like cytogenetic and non-cytogenetic, along with the molecular probes, needs to be included in this biomarker. To apply the DNA-DBs in the future, the perfect integration of both prevailing techniques like cytogenetic and non-cytogenetic, along with the molecular probes, needs to be included in this biomarker. Such perfect integration may lead to automatic detection of both simultaneous and multiple tasks. Along with the hyper-mutable state, it also measures the state of specific mutations found in the causal pathway of cancer. It also provides clear details, regarding which gene performs better correlation through DNA damage events along the causal path of a malignant tumour. The full loop formation is identified as the main challenge, as it may predict the cell phenotype (cancer or normal) from the details that are obtained from array strategies. Equal importance is provided to integrate the gene–toxin interaction with the studies of gene–diet interaction while predicting the outcomes of cancer and DNA damage. The comprehensive technique is combined with the robust techniques to accurately detect the risk of cancer not only from outsized genetic subclass, but also from individuals, which is considered as an ultimate goal.

A large number of latest HCC biomarkers are found in phase 1 or 2 biomarker studies, and a number of tests need to be performed on such biomarkers to decide whether they are suitable for clinical practice. Most of the HCC tumours show heterogeneous nature, which constrains the predictive or diagnostic ability of specific biomarkers. However, none of the HCC carries single optimal biomarkers. Consequently, to maximise the utility of biomarkers, future advances in the use of biomarkers could include the combination of several biomarkers or the combination of biomarkers with imaging, clinical criteria, or other diagnostic, predictive, or prognostic panel laboratory tests. Despite its limitations in performance, AFP is identified as the commonly used biomarker. Since the past few decades, several novel HCC biomarkers have been discovered, but till now, none have gained a large approval in clinical practice. Currently, the development process of a number of biomarkers is under processing, which contains a high efficiency in clinical practice. Both tumours and humans show heterogeneous nature; therefore, the standard single biomarker does not show excellent output. Future research will concentrate on combining biomarkers to provide full diagnostic and predictive ability.

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