Implementing Decision Tree-Based Algorithms in Medical Diagnostic Decision Support Systems

by

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ABSTRACT

As a branch of healthcare, medical diagnosis can be defined as finding the disease based on the signs and symptoms of the patient. To this end, the required information is gathered from different sources like physical examination, medical history and general information of the patient. Development of smart classification models for medical diagnosis is of great interest amongst the researchers. This is mainly owing to the fact that the machine learning and data mining algorithms are capable of detecting the hidden trends between features of a database. Hence, classifying the medical datasets using smart techniques paves the way to design more efficient medical diagnostic decision support systems.

Several databases have been provided in the literature to investigate different aspects of diseases. As an alternative to the available diagnosis tools/methods, this research involves machine learning algorithms called Classification and Regression Tree (CART), Random Forest (RF) and Extremely Randomized Trees or Extra Trees (ET) for the development of classification models that can be implemented in computer-aided diagnosis systems. As a decision tree (DT), CART is fast to create, and it applies to both the quantitative and qualitative data. For classification problems, RF and ET employ a number of weak learners like CART to develop models for classification tasks.

We employed Wisconsin Breast Cancer Database (WBCD), Z-Alizadeh Sani dataset for coronary artery disease (CAD) and the databanks gathered in Ghaem Hospital's dermatology clinic for the response of patients having common and/or plantar warts to the cryotherapy and/or immunotherapy methods. To classify the breast cancer type based on the WBCD, the RF and ET methods were employed. It was found that the developed RF and ET models forecast the WBCD type with 100% accuracy in all cases. To choose the proper treatment approach for warts as well as the CAD diagnosis, the CART methodology was employed. The findings of the error analysis revealed that the proposed CART models for the applications of interest attain the highest precision and no literature model can rival it.

The outcome of this study supports the idea that methods like CART, RF and ET not only improve the diagnosis precision, but also reduce the time and expense needed to reach a diagnosis. However, since these strategies are highly sensitive to the quality and quantity of the introduced data, more extensive databases with a greater number of independent parameters might be required for further practical implications of the developed models.

KEYWORDS: Decision tree; ensemble method; machine learning; classification; computer-aided diagnosis

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St. John's, May 2020
Mohammad M. Ghiasi

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1 INTRODUCTION

The last decades witnessed the utilization of machine learning and data mining approaches for investigating a large number of topics/problems in the realm of different sciences and engineering disciplines. This rapidly developing branch of artificial intelligence encompasses a wide variety of algorithms by which the method learns to perform tasks like regression and classification when exposed to data. Each of these methods has its advantages and disadvantages. In the medical domain, these methods have achieved success for supervised learning tasks. Indeed, many researchers have conducted smart techniques over medical data to uncover hidden knowledge and use them to learn regressors or classifiers for clinical decision making.

Although smart techniques have shown promising performance for medical diagnosis, the success of such algorithms in real-world applications largely depends on the employed data for training and testing the model. Generally, machine learning-based methodologies require massive training datasets to generate an accurate yet reliable model for a correct diagnosis of the unseen cases. As modern hospitals and research institutes are well equipped with different data gathering tools, it is expected that having extensive medical datasets is achievable in the near future.

In addition to the quantity of available data, the quality of the data plays a substantial rule in the development of a reliable model. For imbalanced datasets, the performance of the developed model is towards the class with higher instances. In the case of an imbalanced dataset for a classification task, accuracy is not a good criterion for the performance of presented models. Further to the accuracy, other parameters like sensitivity and specificity are helpful to ensure the classification performance of the models.

Fig. 1.1 illustrates a typical medical diagnostic decision support system (MDDSS). As can be seen, by introducing medical data the MDDSS provides suggestion for healthcare professionals and they can make a decision based on their expertise and the system's output.

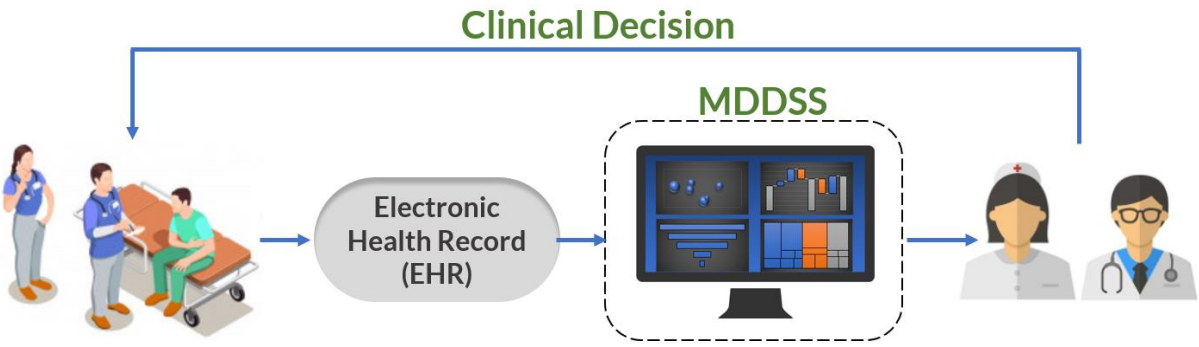

Fig. 1.1: A typical medical diagnostic decision support system

Utilization of machine learning approaches and others statistical pattern recognition models can improve the performance of MDDSSs. This research aims at designing and developing decision tree-based models that can be implemented in MDDSSs. To this end, CART, RF and ET algorithms were employed, and several classifiers were developed for:

- Classification of breast cancer into benign and malignant;
- Diagnosis of coronary artery disease; and
- Selecting a proper approach for wart treatment.

This dissertation consists of a review paper, and three original research works as follows:

- **Chapter 2: A review paper on breast cancer classification (submitted for publication)**

  In the past few years, researchers developed several predictive models capable of classifying breast cancer types. Amongst all publicly available databases for breast cancer, the WBCD is the most widely used dataset to develop BC classification models. Chapter 1 of this thesis aims at identifying the published studies related to the implementation of machine learning and data mining algorithms for WBCD classification. Herein, the developed classifiers based on such algorithms as the artificial neural network (ANN), support vector machine (SVM), fuzzy logic (FL), DT and K-nearest neighbour (KNN), from 1995 to 2020, are reviewed and

analyzed employing statistical parameters namely classification accuracy, sensitivity and specificity.

- **Chapter 3: A research work on the classification of breast cancer (submitted for publication)**

  The first chapter of this thesis presented a review of published classification models for the WBCD. The main goal of this chapter is to evaluate the performance of two ensemble methods, namely RF and ET, in the classification of WBCD. To the best of the authors' knowledge, this is the first work that presents simple visualized models based on the ET methodology in conjunction with the CART method to classify the WBCD. The RF and ET approaches include four main stages; namely input identification, determination of optimal number of trees, voting analysis, and final decision. The models implemented in this research consider important factors such as uniformity of cell size, bland chromatin, mitoses, and clump thickness as the input parameters.

- **Chapter 4: A research work on selecting a proper approach for wart treatment (published in Computers in Biology and Medicine 108, 400-409)**

  In this work, the CART algorithm is employed to develop accurate predictive models capable of analyzing the response of patients having common and/or plantar warts to the cryotherapy and/or immunotherapy methods. To develop a CART classifier for the cryotherapy method, independent parameters including the age and gender of patient, number of warts, type of wart, surface area of warts and the time elapsed before treatment are used. In the case of immunotherapy, in addition to the above-mentioned variables, the induration diameter of the initial test is also considered. To the best of our knowledge, there no research studies in the literature that use CART-based methods for selection of the best approach for wart removal. The primary objective of the present work is to introduce simple-to-employ and accurate

DT-based models that can be used by physicians to select the best treatment method for common and/or plantar warts.

- **Chapter 5: A research work on the diagnosis of coronary artery disease (published in Computer Methods and Programs in Biomedicine 192, 105400)**

  This paper involves a DT learning algorithm, namely CART, for a simple and reliable diagnosis of coronary artery disease, also called ischemic heart disease. Several CART models are developed based on the recently coronary artery disease dataset published in the literature. To the best of our knowledge, this is the first work on the application of CART to study the Z-Alizadeh Sani CAD dataset for diagnosis/classification purposes.

The last section of this dissertation provides the readers with a summary, conclusions, and recommendations for future work.

2 UTILIZATION OF MACHINE LEARNING AND DATA MINING APPROACHES FOR CLASSIFICATION OF BREAST CANCER: A SYSTEMATIC REVIEW

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PREFACE

This manuscript is submitted to … for possible publication.

Main author: Mohammad M. Ghiasi

Contribution: carrying out the literature review**;** writing the original draft**;** revision of the original draft based on the comments of co-author

Co-author: Dr. Sohrab Zendehboudi

Contribution: supervision; providing comments on the original draft; review and editing

ABSTRACT

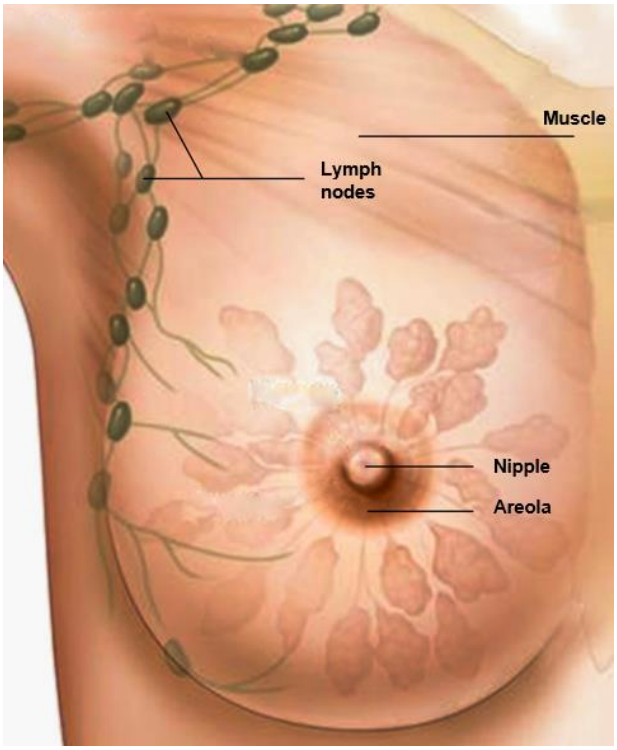
Breast cancer (BC) is one of the most frequently diagnosed cancers among women around the globe. Over the past few decades, several studies have attempted to develop classification models to identify BC by applying machine learning and data mining (MLDM) approaches to both private and public BC datasets. These classifiers can be used for the development of computer-aided diagnosis/ detection (CAD) systems to investigate BC. Up until now, several databases have been provided in the literature to investigate different aspects of BC. Amongst all available BC databanks, the Wisconsin Breast Cancer Database (WBCD) is the most widely used dataset to develop BC classification models. This research aims at identifying the published studies related to the implementation of MLDM algorithms for WBCD classification. Herein, the developed classifiers based on such algorithms as the artificial neural network (ANN), support vector machine (SVM), fuzzy logic (FL), decision tree (DT) and K-nearest neighbour (KNN), from 1995 to 2020, are reviewed and analyzed employing statistical parameters namely classification accuracy, sensitivity and specificity. It was found that some of these techniques are capable of providing excellent results for breast cancer diagnosis. However, to implement these systems on large scales, further analyses should be performed on different breast cancer datasets.

KEYWORDS: Breast cancer; WBCD; classification; machine learning; data mining; computer aided diagnosis; review

2.1 INTRODUCTION

2.1.1 BC Overview

BC occurs in both women and men. However, as opposed to other cancers like lung, prostate, colorectal and stomach, BC is rare cancer amongst men. Nevertheless, this heterogeneous disease is one of the most common cancers amongst females worldwide. The abnormal breast cells are the starting points for BC development. Commonly, BC appears in the ducts, lobules, milk-producing glands and the milk-carrying tubes. The simplified anatomy of the woman adult breast is depicted in **Fig. 2.1**.



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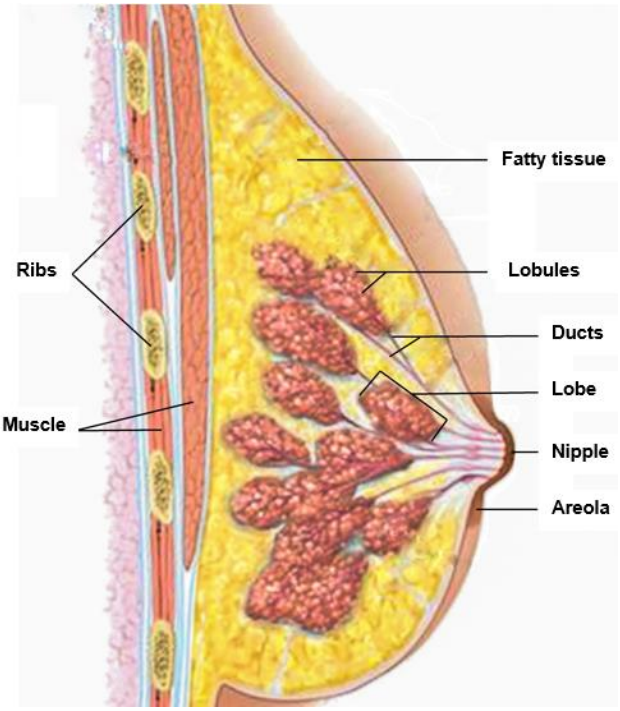
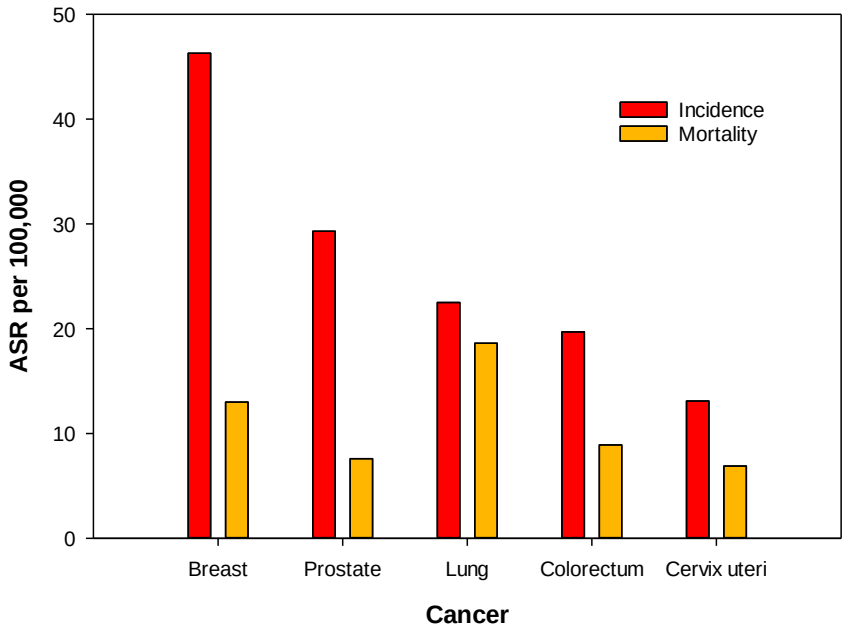


(b)

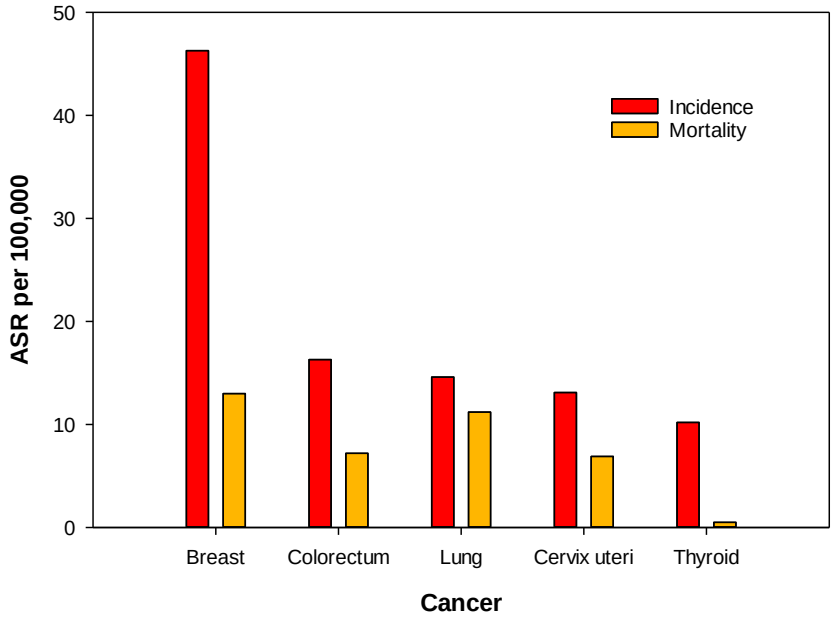
Fig. 2.1: Anatomy of the woman breast; (a) front view; (b) cross section view (Adapted from Ref. [376])

BCs can be split into two main categories: the sarcomas and the carcinomas. Sarcomas, that account for less than 1% of primary BCs [1], are cancers originating in connective tissues of the breast like blood vessel cells and myofibroblasts. As the most common BCs, carcinomas start in epithelial tissues of the breast, i.e. the components that line the terminal ducts and the lobules. In situ and invasive carcinomas are significant types of carcinomas. As pre-invasive carcinoma, in situ carcinoma grows inside of the normal ducts and/or lobules (stages 0 and I). Invasive carcinomas (stages II to IV) are the cancers that have infiltrated the outside of the normal breast ducts/lobules. Invasive cancers may spread to other parts of the body in the way of metastases.

A worldwide estimation of the age-standardized rates (ASR) of incidence and mortality of common cancers in 2018, for both genders and all ages, is depicted in **Fig. 2.2**. As can be observed from **Fig. 2.2(a)**, BC is the most prevalent cancer in the world. Moreover, **Fig. 2.2(b)** shows that this multifaceted and complex disease is the primary cause of cancer death for women.



(a)



(b)

Fig. 2.2: Estimated ASR of incidence and mortality of most common cancers in 2018 (a) worldwide, all ages, both genders; (b) worldwide, all ages, women (Based on the data from GLOBOCAN 2018 [2])

The occurrence of BC for women of all ages in different regions, in terms of incidence and mortality rates, is illustrated in **Fig. 2.3**. **Fig. 2.3** shows that the incidence and mortality rates vary across different regions, ranging between 34.4-86.7 and 11.3-17.2, respectively [2]. Generally, more developed areas, i.e. Oceania, Europe and North America, experience much higher BC incidence rates than other regions, including Africa, Asia, Latin America and the Caribbean. As can be seen from **Fig. 2.3**, the lowest BC incidence rate is found in Africa, but here has the highest BC mortality rate as well.

Studies showed that the incidence of BC has increased over the last decades. However, a research study showed that the survival rate from BC in the previous four decades has risen from 40% to 80% [3]. Another work showed that the five-year survival rate for patients with BC had been increased

from 75% in 1976 to more than 90% in 2017 [4]. Another study indicated that the ASR of BC mortality fell from 33 per 100,000 per year in 1990 to 21.3 per 100,000 per year in 2010, which shows a 36% decline in mortality rate [5]. The improvements in survival rates from BC are commonly attributed to two main lines of thought [5]. A group of researchers believe that mammographic screening yields positive results [6-8]. On the other hand, it is claimed that the decline in deaths from BC is due to the adjuvant systemic therapies [9, 10].

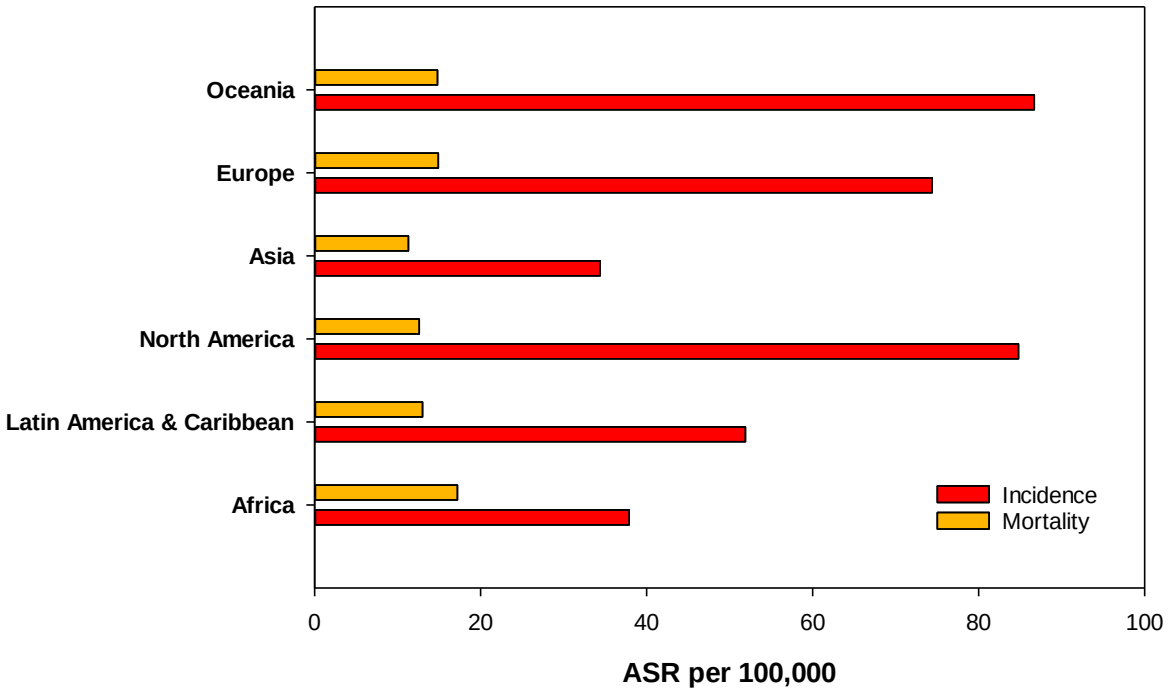


Fig. 2.3: Estimated ASR of incidence and mortality of BC in women in different regions. (Based on the data from GLOBOCAN 2018 [2])

2.1.2 Classification Studies

The last decades witnessed the utilization of MLDM approaches and/or CAD systems for investigating a large number of topics/problems in the realm of different sciences and engineering disciplines. In the case of BC, there are a large number of publications employing methods like ANN, FL, SVM, DT and KNN for developing the classification models and/or CAD systems. There

are publicly available databases for BC. For example, the Mammographic Image Analysis Society (MIAS) digital mammogram database [11], Image Retrieval in Medical Applications (IRMA) databank [12], Digital Database for Screening Mammography (DDSM) [13], WBCD [14] and Wisconsin Diagnostic Breast Cancer Database (WDBC) [15-17].

In addition to the publicly accessible databases, there are various private databanks in the literature. Utilizing these private databases, researchers employed MLDM methods to study breast cancer. For example, researchers employed fuzzy C-means (FCM) to detect suspicious breast tissue regions [18]. The used database included 40 malignant and 21 benign samples. These samples were biopsy-confirmed lesions in 34 female cases. It was revealed that fuzzy-based detection of breast masses, benign or malignant, using appropriate feature sets could provide 100% accuracy. The FCM method was also employed in another study to analyze a private database for breast cancer [19]. The achieved accuracies were around 95%. Schaefer [20] applied the ACO-based classification method to study the breast thermograms (117 benign and 29 malignant samples). The proposed model provided 79.5% accuracy for the test data. In another work [21], the ultrasound images of patients at the University of Chicago Medical Center were analysed using linear discriminant analysis (LDA) algorithm to classify the nodes that were negative for metastasis (114 cases) and nodes that were positive for metastasis (109 cases). Applying multiple discriminant analysis (MDA) on private 363 ultrasound images, the obtained accuracies for invasive carcinomas, non-invasive carcinomas, fibroadenomas and cysts were 88.4%, 80.6%, 86.0% and 84.1%, respectively [22].

Using the KNN algorithm, a study was performed on a database, including 97 ultrasonographic images of the breast at Mie University Hospital [23]. This database has 49 malignant samples and 48 benign cases. In the observer investigation, three breast surgeons (expert) and seven clinicians (general) were employed. It was found that utilization of KNN model as a CAD scheme improved the capability of viewing the probability of the histological classifications of non-mass lesions that appear as the hypoechoic zone in a mammary gland for both the general and expert cases. In another work [24], the KNN technique was applied on a databank of 200 women patients' magnetic

resonance images in order to classify the non-invasive lesion subtype. From the group of 200 women patients, it was identified that 148 lesions were suitable for investigation. For all histological subtypes, including lobular, ductal and DCIS, the accuracy of the KNN classification was about 75%. Studying 234 female patients (149 malignant and 85 benign lesions) by magnetic resonance imaging (MRI) at the Sun Yat-sen University Cancer Center, researchers defined 28 features for each lesion [25]. Then, KNN, SVM and random forest (RF) methods were used to test their classification performance. Using different feature subsets, the average accuracy of the SVM and KNN models was around 80%, and the RF provided an accuracy of about 70%. Both KNN and ANN methods were used to classify a database of mammograms into biopsy-proven malignant mass (80 samples) and masses without cancer (120 samples) [26]. In a research study [27], the ANN model was developed to classify the density of breast tissue using mammograms collected at EL FARABI radiologic center.

For lesion classification, employment of SVM method with different kernels including linear, polynomial, radial basis function (RBF) and sigmoid on a database containing 84 MRI images (23 benign and 61 malignant lesions) was evaluated in the literature [28]. A group of researchers presented a phase-based texture descriptor for discriminating the malignant and benign cases in breast ultrasound images [29]. To this end, the authors employed the SVM approach with the RBF kernel function. The used databank contains 138 images (69 benign samples and 69 malignant samples) that were obtained from Huashan Hospital. Although the proposed model, with around 85% accuracy, provided satisfactory results, this CAD system is not fully automatic. In another work [30], the combined performance of morphological and textural features for detecting the breast masses in 120 ultrasound images was assessed. The used database consists of 50 malignant cases and 70 benign samples. For the classification purpose, a particle swarm optimization (PSO)-based SVM method with RBF kernel was employed that provided an accuracy of higher than 95%. To classify the ultrasound breast tumour images of 90 malignant cases and 120 benign cases, Wu, Lin and Moon [31] employed immune system-based SVM strategy. The proposed classification model

achieved accuracy of 96.7%. Other related works in this regard can be found in the literature [32-135].

2.1.3 Study Objectives

Based on recent research, a large number of deaths happens because of cancers like BC. The most important reason is the detection of cancer at an advanced stage. Hence, early-stage detection of BC is crucial to adopt a proper treatment. As an alternative to traditional approaches for BC investigations, MLDM algorithms have been used in the literature for BC studies. The primary objective of the present study is to review the published works on the implementation of MLDM algorithms and CAD systems for investigation of the BC; in particular, the classification models developed using WBCD.

To this end, the rest of the work is organized as follows: In Section 2.2, the theoretical aspects related to the BC, like factors causing BC, prevention of BC, BC diagnosis methods, imaging modalities for BC and different therapy approaches of BC is presented. Section 2.3 briefly presents a general development procedure of the CAD system for BC. In Section 2.4, the classification models developed based on the WBCD are reviewed. Using some statistical parameters, the performance of the developed classifiers for WBCD is assessed in Section 2.5. The study is concluded in Section 2.6. Finally, Section 2.7 presents the recommendations for future studies.

2.2 THEORETICAL ASPECTS

2.2.1 Factors that Affect BC

The risk factor is defined as anything that increases the chances of developing a specific disease. Generally, the more risk factors an individual has, the higher the chance that he/she gets the disease. However, the presence of a risk factor, and even several risk factors, doesn't necessarily mean that developing a particular condition is inevitable. In other words, the risk factors do not directly cause

disease. Furthermore, risk factors can be categorized as unchangeable and changeable factors. Factors like gender and age are fixed risk factors and cannot be modified, while variable risk factors like smoking and blood pressure can be modified with changing the lifestyle or treatment.

Different risk factors are associated with different diseases like cancers [136]. Leading contributing factors in BC development are known to be as follow:

- *Gender*: the most substantial risk factor for BC is gender (being a woman) [136]. Indeed, around 99 percent of BC cases occur in women [137]. However, BC incidence amongst males has risen 60 percent since 1990 [138]. With an estimated 41000 deaths in 2018, BC has the second-highest mortality rate amongst females [139]. Studies showed that the lifetime risk for women in the UK and the USA of being detected with BC was one in every eight cases [140, 141].
- *Age*: ageing is another considerable risk factor for the development of BC. Getting older increases the likelihood of developing BC. For example, if the current age of a woman is 20, the probability of developing BC in the next ten years is 0.05%. On the other hand, the probability value for a woman of age 70 is 4.14% [142]. Due to the fact that the probability of a female developing BC is dependent on her age, it is suggested to consider the risk estimation at certain ages instead of considering the lifetime risk estimation [138].
- *Family history/genetics*: although more than 85% of women diagnosed with BC do not have a family history of BC, it is believed that women with a family history of BC have an increased likelihood of BC development [143, 144]. In the period from 1950 to 1979, family history was identified as a risk factor for BC [145]. Three main variables are at play in examining the role of family history: the degree of relationship between relatives with BC and the patient (first degree, second degree or beyond), the age of BC diagnosis in the relatives and the history of other genetic factors/cancers that are related to BC [138]. The lifetime risk of BC increases by 40-85% as a result of high penetrance gene mutations called BRCA1 and BRCA2 [146, 147]. In addition to family history, the personal history of BC or

other types of cancers is also known to be a risk factor. Indeed, women who are BC survivors or women with a history of specific cancers have an increased risk of BC development [148].

- *Ethnicity/race*: as can be observed from **Fig. 2.3**, ASRs of incidence and mortality of BC in women vary from region to region. The reasons behind these differences are not well addressed in the literature yet. However, the roles of factors like access to health care, lifestyle and genetics are considered to be important in this regard. For example, it was found that the risk profile of daughters of Asian women who are born in North America are similar to white American women [138].
- *Lifestyle*: studies relate some behavioural factors to the risk of developing BC. For example, the risk of developing BC increases by 30-60% by being overweight [149]. Doing regular exercise is a factor that reduces the risk of BC [150]. The association of tall stature with increased BC risk is also documented in the literature [151]. Alcohol consumption is known as a factor that increases BC risk [152]. Diet is another risk factor that is modifiable [153-155]. Exposure to radiation ranging between 1 and 3 Gy for treatment o some diseases like scoliosis increases the risk of BC in women aged less than 40 years [156].
- *Reproductive and menstrual factors*: high levels of estradiol circulation in the bloodstream increases the risk of BC amongst postmenopausal females [157]. This study also showed that girls who began menses after age 15 have a decreased risk compared with girls who started before age 12 [157]. There is a slight increase in BC risk for the first ten years after the delivery of the baby. However, eventually, BC risk decreases to below that of a female without children. Furthermore, breastfeeding leads to a reduction in BC risk [138]. The protection from BC is even better if women breastfeed for more than 25 months [158]. Studies also revealed a relationship between the use of hormone replacement therapy and BC risk [159]. Females with high bone density are considered at higher risks for BC [160]. More considerable amounts of connective and milk duct tissues in the breast, i.e. higher breast density, is found to increase the risk of BC [159].

Identification of BC risk factors and, consequently, underlying the impact of each of them on developing BC is a crucial task. The widely available way to reduce the risk of BC is the implementation of proper lifestyle modifications according to the impacts of modifiable risk factors. In addition to the lifestyle modifications, chemoprevention and genetic counselling are other strategies for BC risk reduction. Furthermore, one of the most critical actions that should be taken is following the early detection approaches and guidelines. Although early detection of BC does not prevent the disease, it increases the chances of successful treatment.

2.2.2 Methods for BC Diagnosis

Early detection of BC improves the likelihood of survival and increases the possible options for treatment as well. Furthermore, early BC detection reduces treatment expenses [161]. Currently, average treatment costs for stages 0, I, II, III and IV are $60637, $82121, $82121, $129387 and $182655, respectively [162]. Several screening approaches are proposed in the literature for the detection of BC. According to the Canadian Cancer Society [163], screening is defined as checking for a particular disease in a group of individuals who have no symptoms of the disease. The manual self-examination is the most straightforward and widely available technique for BC screening. In this method, every breast is palpated for abnormal lumps and distortions [161]. As the self-examination can detect up to 50% of asymptomatic BCs [164], monthly self-exam is recommended by the American Medical Association. However, studies have shown that this method might lead to a high rate of false positives. As a result, women who practice self-exams may experience depression and anxiety [161].

Several image modalities can be utilized for examination of the breast for probable cancer. In general, these imaging modalities are helpful for precise analysis of certain facets of breast tissue organs. The most common choice in clinical practice is the mammography that employs low-dose x-rays. Since mammography might be less accurate for women with dense breasts [165], ultrasound

imaging can be considered as a proper modality [166]. To form pictures of the whole breast volume, the magnetic resonance imaging (MRI) technique can be utilized. Other conventional image modalities are infrared thermography and microscopic imaging. The rest of this section gives a brief introduction to the mammography, ultrasound and MRI modalities for BC screening.

A typical mammographic picture of a woman's breast is shown in **Fig. 2.4**. Although mammography is a low-cost proper screening method for BC, mass detection in mammograms could be challenging. This is owing to the fact that masses available in different sizes, shapes and margins [167]. Moreover, masses are often indistinguishable from their surrounding tissues [168, 169]. Over the past years, more efficient mammography systems were introduced. The replacement of x-ray films by electronics is the most significant improvement in this regard. This technique, called digital mammography or full-field digital mammography (FFDM), needs a lower radiation dose and provides better pictures [170]. For women aged under 50 years, FFDM found to be more accurate [165]. Some studies indicated that BC detection rate with FFDM is more than 4.2 per thousand mammograms [171, 172].

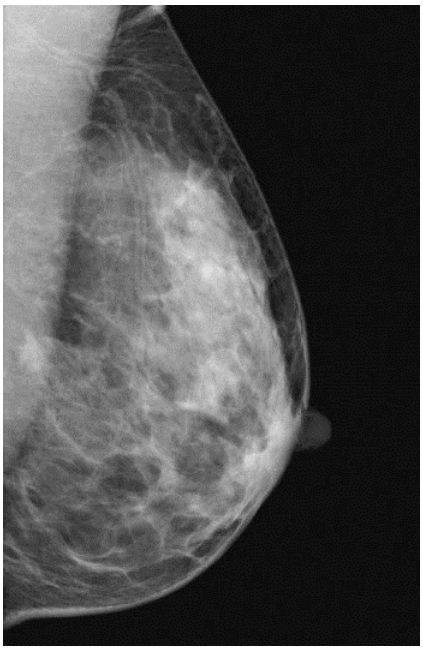


Fig. 2.4: A mammographic picture of a woman's breast (adapted from Ref. [377])

For women with dense breasts, breast ultrasound is suggested as a proper alternative for mammography. As an advantage over the mammography, the ultrasound modality is a radiation-free approach and patients well tolerate it [45]. However, according to a report by the American College of Radiology Imaging Network [173], the combination of mammography and ultrasound methods improves the BC detection. To perform high-quality breast ultrasound, the American College of Radiology (ACR) standards established professional guidelines that cover technical parameters, equipment, personnel and image annotation [174]. Based on the ACR standards, Baker and Soo [175] assessed the imaging appearance and technical quality of breast sonograms. In **Fig. 2.5,** a sample of the ultrasound images is depicted.

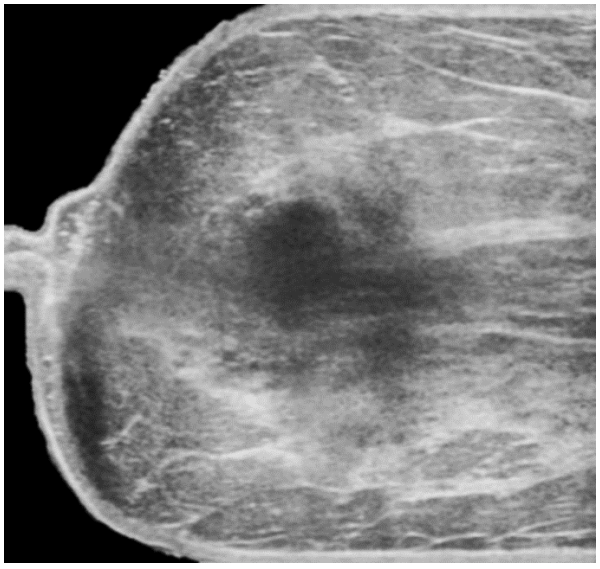


Fig. 2.5: A picture of a woman's breast captured using ultrasound modality (adapted from Ref. [378])

Another valuable tool for assessment of the BC is MRI. **Fig. 2.6** shows an image of a woman's breast generated using the MRI.

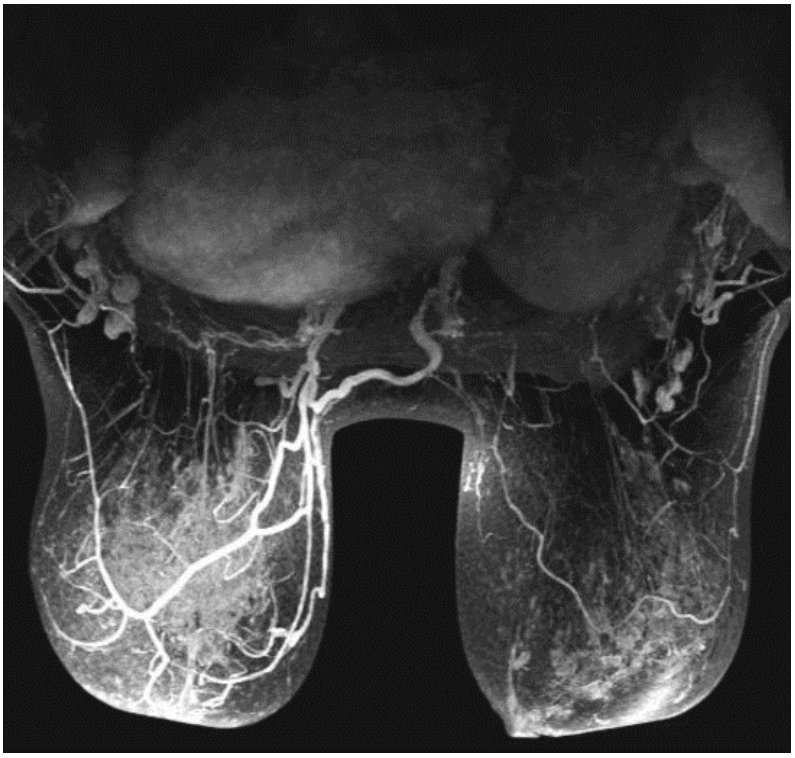


Fig. 2.6: A picture of a woman’s breasts obtained via MRI (adapted from Ref. [177])

This imaging modality that entails injecting the contrast medium in the patient's body is often utilized in high-risk cases. Furthermore, this technique is a good tool to evaluate the newly detected BC before operation [176]. Indeed, MRI enables us to get more information on probable deep involvement, and it is capable of revealing signs of chest structure and underlying muscles' inflammation [177]. The sensitivity of the MRI modality in BC ranges between 85 and 100%. As a result, this technique is efficient in excluding the BC recurrence in cases without any access to image the primary tumor region on mammography [178]. On the other hand, since the specificity of this imaging modality may be moderate (ranged from 60 to 90%), it can be impossible to define the tumor’s origin, i.e. malignant or benign [178-180]. For breast MRI with final evaluations that are connected to suggestions for care, a lexicon is provided by the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) [181].

Further to the above, positron emission tomography (PET) is another tool that visualizes the areas of higher metabolism in the region of interest. In this method, the body receives a slightly radioactive sugar; consequently, more tracer substance is absorbed by the tissues having a higher metabolism. Compared to other tissues, tissues with higher metabolic rates show brighter [161]. Utilization of the PET technique in combination with the computed tomography plays a progressively significant role in all facets of BC like staging, curative treatment as well as follow-ups [182, 183]. PET-CT method has high sensitivity in the detection of primary breast tissue. Furthermore, this technique has revealed high specificity as well as a high positive predictive value [184]. Surgical options are also available for the diagnosis of BC [185].

2.2.3 Therapy/Treatment Methods of BC

A range of treatments and therapies are available to deal with BC. However, decision making regarding the BC treatment approach for each patient is a multidisciplinary task, and all the cons and pros of the possible options must be discussed before finalization of the plan [186]. Due to the discussions of tumor board about the patient status, the mortality from BC has been reduced [187]. Biometric data of the patient like age, height and weight is an essential factor that must be taken into account to design a BC treatment plan. The tumour size and biological characteristics, cancer type, involvement of axillary nodes as well as nearby regions like the breast skin, estrogen receptor, metastases and also the financial status of the patient are some other important factors in this regard [188]. The main approaches for BC treatment are surgery, radiotherapy, chemotherapy, hormonal therapy and targeted therapy. In some cases, a combination of these treatments may be utilized.

Nowadays, the surgical approach is the central aspect of BC therapy and treatment, as it was before. The primary treatment modality for the majority of females diagnosed with early BC is the surgical option [3]. Generally, mastectomy and breast-conserving surgery are the two fundamental types of this treatment approach. The form of surgery is substantially associated with the size of the tumor [188]. In cases that the tumour is too large, the surgery is in the form of mastectomy. However,

breast-conserving surgery can be utilized if the neoadjuvant chemotherapy could shrink the tumour to small enough size [136]. For early-stage invasive carcinomas, breast-conserving surgery is the most fundamental part of the patient's treatment [189-191]. After the mastectomy, the next essential step of the procedure might be the breast reconstruction that has emotional and psychological benefits to the patients [192, 193].

Generally, BC treatment consists of surgery with or without systemic therapy like hormonal therapy and chemotherapy and with or without radiation. Systemic therapy might be applied before surgery (known as neoadjuvant) or after surgery. If the systemic therapy must be administered after the surgery, it might be employed after radiation, concurrent with radiation or before radiation [138]. For the systemic chemotherapy, there are several regimens that typically contains a taxane and an anthracycline [194-196]. Patients with HER2-positive BC are treated utilizing chemotherapy in combination with targeted therapy [197]. For patients with stage I HER2-positive BC, employing the paclitaxel with trastuzumab is a common regimen [198]. For stage II and II HER2-positive BC, the standard is the administration of dual-HER2 agents [199]. Commonly, endocrine therapy is recommended for patients with HR-positive BC [200].

Cancer treatments might have physical and psychosocial side effects. Fatigue, pain, nausea, changes in skin and nail, appetite changes, loss of sex drive, fertility issues in females, memory and sleeping problems, nerve problems and changing body image are some common side effects on the physical status of the patients [201]. Psychosocial side effects of BC are related to the psychological, lifestyle and social aspects of the patient [188]. Complementary therapies can be helpful in the effective management of the BC treatment side effects and the recovery process. This type of therapy (like music and energy therapy, hypnotherapy, acupressure, meditation, etc.) is not part of/alternatives to the medical treatments [188]. Since the recurrence of BC after the treatment procedures is probable, surveillance of BC survivors is a crucial part of their care. American Society of Clinical Oncology (ASCO) developed the guidelines for post-treatment surveillance in BC [202].

2.3 CAD SYSTEMS FOR BC STUDIES

2.3.1 Development Procedure

The development of CAD systems for investigation of the BC is considered as a practical approach to detect masses and classifying them as well. Indeed, CAD systems are beneficial, helping experts to interpret the breast images (mammogram, ultrasound, MRI, microscopic, or infrared thermography). Research showed that CAD-based approaches are being more accurate as the MLDM methods and related areas are developing [203, 204]. Since the majority of the published studies utilized mammograms to detect BC via CADs, this section overviews the CAD development procedure for mammograms. It is worthwhile to mention that CAD in mammograms was approved by FDA in 1998 [205].

Considering the mammograms, the CAD systems can be employed to classify the mammographic lesions into malignant or benign mass. There are several main steps in the development of a typical CAD system for breast mass detection and classification. **Fig. 2.7** schematically demonstrates a typical CAD, which includes four main stages, for the application of interest. CAD also can be divided into two parts, namely computer-aided detection (CADe) and computer-aided diagnosis (CADx). Utilizing CADe, such abnormalities in breast lesion as clustered masses and micro-calcifications can be detected. Then, the CADx is used to classify the detected anomalies. Finally, the computer flags the regions of concern on the image [206].

As can be observed from **Fig. 2.7**, the first step is the digitization of the mammograms and pre-processing the images. As shown in **Fig. 2.8**, and having the anatomy of the breast (**Fig. 2.1**) into consideration, it is demonstrated that the dense tissues, like glandular, are represented by bright areas, and the less tense tissues, like fatty, are less bright. Generally, the brighter areas have higher noise levels. In other words, different brightness levels in different sections of the image produce some noise. Hence, the pre-processing step should be performed for decreasing/ equalizing the noise

level in mammograms and improving the image's contrast. Proper pre-processing substantially increases the success probability in the next steps of CAD design for breast cancer study.

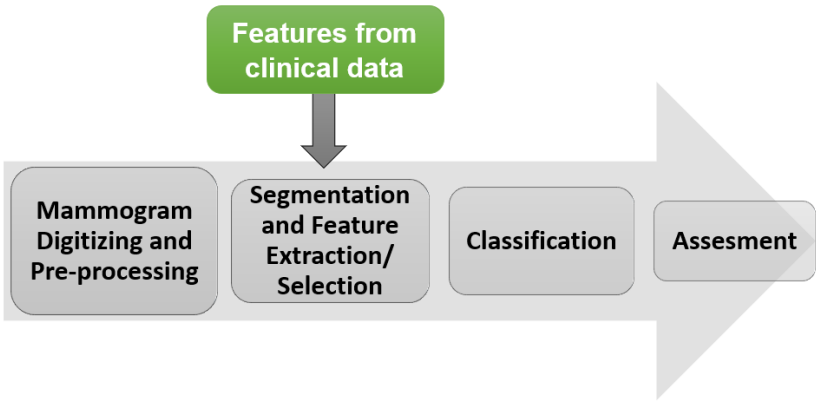
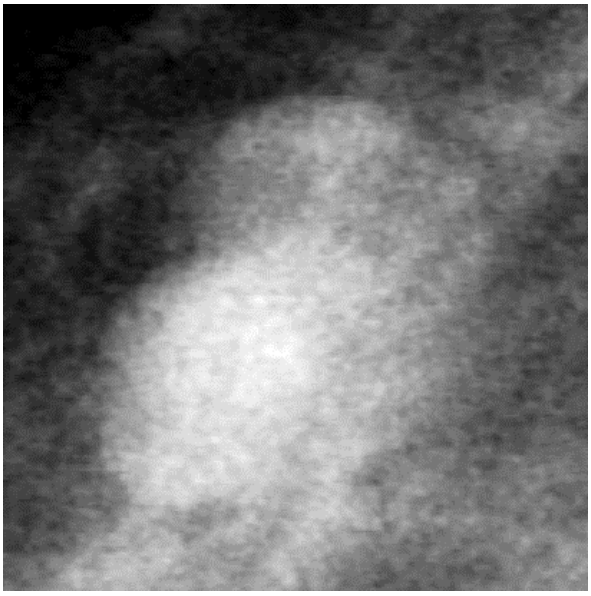
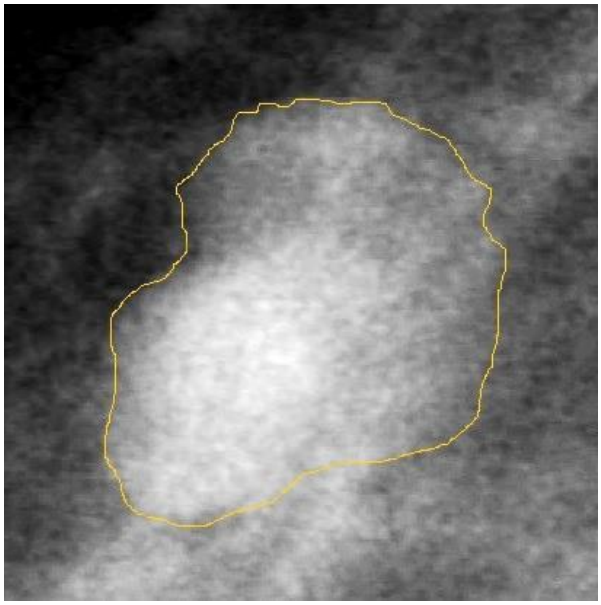


Fig. 2.7: Schematic of a typical mammogram-based CAD system for breast mass classification

Since most mammograms are high resolution and large size images, applying a size reduction technique is usually done during the pre-processing step. The detailed information regarding the mammogram pre-processing can be found in the literature [207-214].



(a)



(b)

Fig. 2.8: (a) A typical ROI showing a mass in the mammogram; (b) mass segmentation from the tissue of the background (adapted from Ref. [379])

The segmentation phase can be defined as the separation of the main sections from the other parts of the image. Indeed, the contours of the suspected lesion, or region of interest (ROI), are identified and separated to define meaningful regions for speeding up the next steps of CAD system development. **Fig. 2.8** demonstrates a sample of mass segmentation from the tissue of the background in a mammogram. However, due to the problems like homogeneity between breast and pectoral tissues, imperfections in the process of mammograms scanning, tags and light leakages, this step is a challenging task [215, 216]. There are many methods and techniques in the literature proposed for the segmentation of mammograms [217-233].

The segmented regions, then, are employed to extract out the features. These features that are quantitative measures are the primary representative of the mammograms of the breast. A variety of feature extraction methods have been used and evaluated in the literature [77, 234-243]. As opposed to feature extraction methods that build a new set of attributes via combining the existing features, a value of importance is assigned to each feature in the feature selection algorithms [244]. Indeed,

the feature selection methodologies eliminate the redundant and irrelevant features from the original set [245]. As a result, the informative features are selected for the classification phase.

The next primary step in the development of a CAD system for BC is the classification. In this phase, corresponding to a malignancy/benignancy and/or the lesion type, the vector of features is labelled as a specific class. The previous steps directly affect the accuracy of the classification process. ANNs, SVMs, FL, adaptive neuro-fuzzy inference system (ANFIS), KNN, DTs and Naïve Bayesian (NB) are good examples of classifiers that can be used to perform the classification task. The constructed model can be utilized for the prediction of future samples. The final step in the CAD system development can be defined as the assessment stage. The purpose of this step is to evaluate the accuracy and robustness of the developed CAD system for the investigation of BC.

2.3.2 Software and Computational Tools for BC Classification

Several data mining tools and software are available that can be utilized for BC investigations. Waikato Environment for Knowledge Analysis, also known as Weka, is free software that has an assortment of modeling and visualization techniques. Data mining and modeling tasks like data pre-processing, data visualization, feature selection, regression, classification and clustering can be performed using Weka. Orange is another toolkit for MLDM and data visualization. This open-source component-based visual programming software can be used as a Python library for widget alteration and data manipulation. KNIME provides an easy to implement tool for fast data exploration. As a new platform for data analytics, KNIME has a wide variety of machine learning algorithms, from decision trees to deep learning networks, for predictive modeling. Another free suite of MLDM approaches for researchers is Tangara. This tool consists of techniques and algorithms for instance selection, feature selection and construction, descriptive statistics, data visualization, classification, clustering, regression and association rule learning.

2.3.3 Current Status and Future Prospects of BC Classification

The last decade witnessed an increase in applying different MLDM techniques like ANNs, SVMs, fuzzy logic and evolutionary algorithms for BC investigations. As a result, the diagnosis of BC, especially at the early stages, has boosted up. However, there is still a need for better models in terms of accuracy, precision and speed.

Amongst the available MLDM methods, deep learning showed a good potential for solving regression, classification and pattern recognition problems. The deep learning approach provided satisfactory results, especially in tasks related to image processing. This is owing to the fact that this approach enables the user to capture even the smallest changes in images. This feature is very vital in tasks like BC detection/classification. Besides all the advantages that deep learning has to offer for BC studies, some considerable drawbacks are associated with this approach. Indeed, a large amount of data is required to develop predictive models based on deep learning. Furthermore, due to its complex data models, training a system using deep learning can be expensive.

2.4 WBCD CLASSIFICATION STUDIES

2.4.1 WBCD: An Overview

This section briefly introduces the WBCD. The WBCD, originally reported by Dr. William H. Wolberg at the University of Wisconsin Hospitals in Madison [14], presents some measurements related to BC. This databank is provided in accordance with the FNAB data [246]. Each dataset of this database comprised of nine cytological characteristics of benign or malignant breast fine-needle aspirates. The WBCD has a total number of 699 records where 458 (65.5%) datasets are defined as "benign," and 241 (34.5%) datasets are classified as "malignant."

Excluding the ID number, each dataset of the WBCD has ten attributes, nine of which are independent parameters and the breast cancer type, i.e. benign or malignant, is the dependent

parameters. Each independent characteristic is graded with a value that ranges between 1 and 10. In respective order, 1 and 10 indicate the typical benign and typical malignant. There are 16 datasets in the WBCD with missing values. The remaining datasets contain 444 benign and 239 malignant cases. Further information about the WBCD independent attributes is given in **Table 2.1**.

Table 2.1: Information about the refined WBCD

Feature	Range	Average
Uniformity of Cell Size	1-10	4.442
Uniformity of Cell Shape	1-10	3.151
Bare Nuclei	1-10	3.215
Single Epithelial Cell Size	1-10	2.830
Bland Chromatin	1-10	3.234
Normal Nucleoli	1-10	3.545
Clump Thickness	1-10	3.445
Marginal Adhesion	1-10	2.870
Mitoses	1-10	1.603

From the early nineties, a great number of modeling attempts have been made by implementing different MLDM algorithms to analyze the WBCD. In this section, the published works on the classification of breast cancer based on the WBCD using various MLDM techniques such as ANNs, FL and SVMs, from 1995 to 2020, are reviewed. It should be noted that although ANNs and SVMs, as the most employed approaches in BC classification, can be used for performing nonlinear modeling, they mainly have a "black box" nature. Indeed, ANNs and SVMs do not provide detailed insights into the mathematical formulation/structure of the function. Moreover, these techniques, in general, suffer from overfitting problems. Being stuck in multiple local minima is another serious drawback for a majority of connectionist tools. To improve the accuracy of the modeling, the

methods might be implemented in conjunction with various algorithms such as genetic algorithm (GA) and PSO. Besides, the models appear to be complicated.

2.4.2 ANN-Based Models

ANN frameworks are able to learn to do assignments by pondering models, generally without being programmed by task-explicit guidelines. ANNs are trainable even with deficient information. However, ANNs give a superior exhibition when there is an extensive dataset for training. These algorithms have the ability to break the main problem into simpler ones. On the other hand, ANNs function as a black box. Furthermore, there is no universal method for deciding the structure of an ANN.

Using a neural network (NN) pruning algorithm, Setiono [247] presented three-layer feed-forward (FF) ANN models having a different number of neurons in the hidden layer. Then, some rules were extracted from the developed NN models for the diagnosis of breast cancer. Setiono and Liu [248] used a standard FF-ANN to obtain the most useful attributes of the WBCD for defining the breast cancer classes. For this database, 30 ANNs with 12 hidden neurons were created. Results suggested that the performance of the network can be increased using about one-third of the total input features. Unfortunately, the selected input features are not reported in this study. In another study, Setiono and Liu [249] compared the DT and three-layer FF-ANN rules for the WBCD. Amongst the available DT methods, the authors employed the C4.5 model [250]. Although the FF-ANN slightly provided better results than the DT, the neuron-based model has more rules than the DT. The number of extracted rules from the ANN and DT models were seven and four, respectively. Moreover, using the DT produces interpretable rules. However, the ANN models are commonly known as "black-box" models that are hard to interpret. As a continuation of the published series on the application of FF-ANN method for WBCD classification, Setiono [251] investigated the influence of the data pre-processing on the accuracies of both the networks and the associated rules (the rules extracted

from the developed networks). First, the datasets with missing values were discarded from the databank. Second, the most relevant independent parameters of the WBCD were selected for classification. It was found that data pre-processing improves the performance of the networks and the extracted rules for the problem of WBCD classification.

Further to the above, Taha and Ghosh [252] introduced an extracted rule-based system using the ANN strategy. Then, they integrated the trained ANN model and the rule-based system to improve classification accuracy. Indeed, the authors employed three methods to extract rules from trained FF-ANNs, including the binarized input-output rule extraction (BIO-RE), partial-RE and full-RE. The use of four different NN architectures, including the multi-layer perceptron (MLP), RBF, a mixture of experts (MOE) and general regression (GR) network for the breast cancer classification, was evaluated by West and West [253]. Results showed that all these methods approximately provide the same accuracies. The MLP-ANN method, in combination with a learning algorithm that applies linear least square, is also used in a different study as the classifier for the database of WBC [254]. The authors compared the proposed linear algorithm with four well-known learning algorithms: gradient descent (GD), gradient descent with adaptive momentum and step sizes (GDX), Levenberg-Marquardt (LM) and scaled conjugated gradient (SCG). The best results in terms of accuracy, as well as the processing speed obtained from the GDX methodology. However, the speed of the proposed linear algorithm found to be better than GD, LM and SCG techniques. In summary, this linear method offers an acceptable combination of simplicity, accuracy and speed. Utilizing three models, including RBF, MLP and probabilistic NNs, Azar and El-Said [255] classified the WBCD into two categories. Amongst the presented models, probabilistic ANN provided the best outputs.

Using a particular type of MLPs, namely artificial metaplasticity (AM) MLP algorithm, a classification model/approach was developed by researchers to deal with the information of WBCD [256]. The developed AM-MLP, then, was compared to the classical back-propagation (BP) ANN. According to the outcomes, the AM-MLP is superior to the BP-ANN training in all samples.

Application of several BP algorithms including the batch gradient descent (BGD), Quasi-Newton (QN), batch gradient descent with momentum (BGDM), resilient back-propagation (RBP), LM and conjugate gradient (CG) in WBCD classification was also evaluated in some other literature studies [257, 258]. In addition to the BP-ANN, Šter and Dobnikar [259] tested a special type of ANNs known as learning vector quantization (LVQ) for the WBCD case. Classification and regression tree (CART), LDA, quadratic discriminant analysis (QDA), KNN, look ahead feature construction (LFC), assistant-I (ASI), assistant-R (ASR), NB and semi-Naïve Bayesian (SNB) are other employed methods in this study. Based on the error analysis, the QDA model provided the lowest accuracy. Other developed models have approximately equal performance. Janghel, Shukla, Tiwari and Kala [260] implemented several ANN algorithms, including BP-ANN, LVQ, recurrent ANN (R-ANN), RBF-ANN, probabilistic ANN (P-ANN) and competitive learning (CL) ANN for the breast cancer classification. LVQ, big LVQ, and artificial immune recognition system (AIRS) were applied to the WBC database by Goodman, Boggess and Watkins [261].

Three classification models using BP-ANN, real coded GA, and binary-coded GA were presented by Örkcü and Bal [262]. Results showed a better performance of the real code GA over other investigated algorithms. Implementing the GA and adaptive resonance theory (ART) ANN, Punitha and Santhanam [263] studied the classification of the breast cancer datasets. In their proposed model, the dimension is reduced by GA and the ART implemented with the reduced parameters. In another study [264], a wavelet ANN (W-ANN), that combines NN and wavelet transform, was trained with the GA for WBCD classification. Indeed, the excitation function of NN is the wavelet and optimization of the weights was done using the GA algorithm. For the breast cancer prediction, Ahmad, Mat Isa, Hussain and Sulaiman [265] used a combination of a multi-objective GA-based Pareto-optima and ANN (GA-MOO-ANN). Senapati and Dash [266] developed local linear wavelet ANN (LLW-ANN) and RBF-ANN models for breast cancer data's classification. The parameters of the LLW-ANN model was optimized using a recursive least square (RLS) method. The Kalman filter and RLS were employed to find the BP-ANN parameters. Beside the ANN, Liou and Chang

[267] utilized GA, LR, and C4.5 to forecast the breast cancer. Ahmad, Mat Isa, Hussain, Osman and Sulaiman [268] implemented the GA linked to the ANNs trained with BP, LM, and GD algorithms on the WBCD.

For the case of WBC classification, Huang, Hung and Chen [269] used a PSO optimization algorithm to train the ANN system. Moreover, the authors presented two case-based reasoning (CBR) classifiers as well as an ANFIS model. To assign the attribute weights for CBR models, C4.5 and logistic regression (LR) were employed. Malmir, Farokhi and Sabbaghi-Nadooshan [270] developed MLP-ANN models using the PSO method and imperialist competitive algorithm (ICA). They also presented traditional genetic classification (TGC) and classification rules mining model with GA in cloud computing (CGCRMM) models. Leema, Nehemiah and Kannan [271] optimized the ANN classifier using differential evolution PSO and GD-based BP. Senapati, Panda and Dash [272] employed the RBF-ANN classification model. They used KPSO and extended Kalman filter (EKF) to initialize the centers and variances of the network. For updating these parameters, the BP algorithm was utilized.

For the BC classification, Abbass [273] utilized the memetic pareto (MP) ANN, which is a category of evolutionary neural network models. Verma and Hassan [274] proposed two categories of a hybrid combination, including parallel neural-based strong clusters fusion (PNSCF) and parallel neural-based clusters fusion (PNCF) for classification of the breast cancer databank. Moreover, the MLP, k-means and self-organizing map (SOM) models were also investigated.

Employing the rotation forest (RF) ANN, Koyuncu and Ceylan [275] proposed an ensemble classifier. In this model, the principal component analysis (PCA) is used as the feature selector. Furthermore, they presented another PSO-based classifier for breast cancer detection Uzer, Inan and Yılmaz [276] studied the WBCD for classification, through implementing ANN and two hybrid feature selection methods namely sequential forward selection (SFS) and sequential backward selection (SBS). In another work [277], both the generally optimized (GO) ANN and BP-ANN

methodologies were utilized. Nahato, Harichandran and Arputharaj [278] investigated the WBCD using rough set theory (RST) combined with BP-ANN. Implementation of the artificial meta-plasticity (AM) in MLP at the artificial neuron learning level for the diagnosis of breast cancer data is investigated in a research study [279]. In addition to an ANN model, Tsai, Lu, Wu and Lee [280] developed three different ANN-based hybrid classification systems for breast cancer cases: association rule-based ANN, GA-based ANN and correlation-based ANN. A stimulus-sampling technique for boosting the BP-ANN was introduced by Gorunescu and Belciug [281]. The presented model, denoted as BPSS-BP-ANN, is a hybrid model combining the MLP and stimulus-sampling algorithm. This model, then, was compared to the SVM, NB and KNN models. Abdel-Zaher and Eldeib [282] suggested a breast cancer classifier employing a deep belief network (DBN) unsupervised path or randomly initialized weight (RIW) network followed by an LM or CG algorithm. A hybrid model of BP-ANN and NSGA-II algorithm was also developed by Ibrahim, Shamsuddin and Saleh [283] for classification of breast cancer.

In 2020, Korani and Mouhoub [284] implemented a deep feed-forward neural network (DFNN), mother tree optimization (MTO), MTO algorithm with climate change (MTOCL) and PSO for classifying the WBCD. Using a two-step feature selection algorithm in conjunction with ANN, Rahman and Muniyandi [285] developed a classification model.

2.4.3 SVM-Based Models

In the SVM method, which is a supervised learning algorithm, the principal thought is to discover the isolating hyperplane that can amplify the edge of the training dataset ideally. The objective is to increase the space between the closest points to each class and the hyperplane that prompts an ideal breaking hyperplane. It works effectively on datasets with smaller training data as well as linearly and nonlinearly splittable datasets. However, SVMs are not the best choice for working on large datasets because of the high training time and exhaustive computations.

Bennett and Blue [286] made an effort to generalize the SVMs to DTs. The proposed method is something between a univariate DT and a single SVM. Indeed, for each DT in the tree, a SVM was employed. The developed method was then applied to several databanks like WBCD. Based on the results for WBCD classification, however, the SVM model provided the best outcomes as compared to C4.5 and OC1 as DTs and global tree optimization (GTO) and GTO-SVM. Polat and Güneş [287] used the least-squares version of SVM (LS-SVM) for the classification of breast cancer. They employed RBF kernel functions. Subashini, Ramalingam and Palanivel [288] developed SVM and RBF-ANN models for the same goal, i.e. WBCD classification, where a polynomial kernel function was employed. Using the WBCD, Akay [289] presented a SVM-based classifier model with the feature selection utilizing F-score. The used kernel function was a RBF kernel. Similarly, employing FS feature selection method and SVM algorithm, WBCD is classified in another work [290]. Furthermore, the authors also presented a SVM-based model using kernel FS.

Using the Gaussian kernel function, Chen, Yang, Liu and Liu [291] developed a SVM classifier coupled with a rough set reduction algorithm for removing the redundant features/points of the database. Stoean and Stoean [292] utilized the SVMs and evolutionary algorithms (EAs). The authors presented four different models for WBCD classification: SVM, cooperative coevolution (CC), pedagogical CC-SVM and decompositional CC-SVM. In another study [293], The SVM-based model was developed for breast cancer classification through using polynomial and RBF kernel functions with varying arguments (poly order, BoxConstraint and RBF-sigma). In different research studies, automated diagnostic systems, including various types of ANNs as well as SVMs, were implemented by Übeyli [294] and Shahare and Giri [295] for detection of BC type using the WBCD.

For simultaneously solving the feature selection and model selection in SVM, a literature study suggested the PSO optimization algorithm [296]. To control the global and local search in PSO, the authors employed the inertia weight and time-varying acceleration coefficients. Ibrikci, Ustun and Kaya [297] presented the SVM classifier using the exponential-Gaussian combined kernel functions

for breast cancer. Employing a sigmoid kernel function, Zheng, Yoon and Lam [298] developed a hybrid model of SVM and K-means for the WBCD problem (denoted as K-SVM).

In a comparative study conducted by Vig [299], the effectiveness of SVMs, ANN, RF, and NB in classifying breast cancer was evaluated. In addition to the SVM technique, Bashir, Qamar and Khan [300] presented several classification models, including NB, Gini index-DT, DT using information gain (IG), and memory-based learner (MBL). SVM, MLP-ANN, RBF-ANN, C4.5, RF, and the rotational forest were employed in a systematic study by Aličković and Subasi [301] for dealing with the BC databanks.

Based on employing kernels with feature spaces composed by logical propositions, Polato and Aiolli [302] presented an approach, namely BK-SVM, to extract explanation rules from SVM. Mao et al. [303] proposed the transformed ensemble learning (TrEnL) technique for breast cancer classification. They also compared seven ensemble methods, including bagging, AdaBoost, weighted majority vote (WMV), NB, evolutionary ensemble classifiers (EVEN), combining classifiers by using correspondence analysis (SCANN) and MDM. The authors used SVM and CART as base learners in their experiments. Abdar and Makarenkov [304] presented several classifiers based on SVM and ANN algorithms.

2.4.4 Rule/Fuzzy-Based Models

Among real-world problems, there are several cases in various fields with a level of uncertainty and vagueness. The rule/fuzzy-based modes can be implemented for this type of problems. Generally, in a fuzzy rule-based system, the fuzzy sets are used in a way that demonstrate various forms of knowledge about the problem. The simple reasoning process in these algorithms enables them to save computing power. However, lots of data and expertise are required to develop a fuzzy system model.

Several works in the literature proposed rule/fuzzy-based methods in engineering, science, and medicine disciplines for screening, diagnosis, prediction, and classification. Hamilton, Shan and Cercone [305] applied a rule induction algorithm based on the approximate classification (RIAC) method to induce the rules from the database. The accuracy of the RIAC model was then compared to that of the C4.5 method. Peña-Reyes and Sipper [306] presented fuzzy systems in combination with the GA algorithm for WBCD classification. The applied GA defined four main parameters, including input membership function (MF) values, antecedents, relevant variables and consequents of rules. The reasoning mechanism of the proposed models (we denote the models by GA-FLs) was based on Takagi-Sugeno-Kang fuzzy system. In another study [307], the employed fuzzy systems were combined with evolutionary algorithms for breast cancer diagnosis. The authors used a singleton-type fuzzy system for the models. Mallinson and Bentley [308] used a hybrid fuzzy-genetic programming (GP) methodology to discover patterns in the WBCD. In a research investigation carried out by Nauck and Kruse [309], a neuro-fuzzy system, namely NEFCLASS, was developed to obtain classification rules from the WBCD.

A fuzzy classifier based on a fuzzy entropy measure, known as a fuzzy entropy-based fuzzy classifier (FEBFC), was proposed by Lee, Chen, Chen and Jou [310] for the BC pattern classification. In a literature study [311], a methodology was described for extracting the crisp and fuzzy logical rules from WBCD. This method was obtained by changing the MLP network into a logical network (LN) that called MLP2LN. C-MLP2LN method starts from a single neuron and builds the LN employing training data points directly. Authors also proposed two more methods, namely separability split value (SSV) and feature space mapping (FSM).

A fuzzy classifier structure was developed by Abonyi and Szeifert [312] on the basis of the unsupervised Gath-Geva clustering technique. The proposed approach can be considered as an extension of the quadratic Bayes classifier. Based on fuzzy subsethood measurements, Rasmani and Shen [313] conducted quantifier-based fuzzy modeling to classify the breast cancer database. They compared the accuracy of the proposed approach, denoted by FuzzyQSBA, to that of weighted

subsethood-based algorithm. As an adaptive fuzzy pattern classification method, an influential rule search scheme (IRSS) was applied to the breast cancer classification problem by Chatterjee and Rakshit [314].

An ANFIS classification strategy was proposed in the literature [315] as a diagnosis system on the WBCD. In addition to the ANFIS models, the authors also developed several AdaBoost models for comparison. In this study, three different methods were used as a dominant input selector: GA algorithm, DT learning and correlation coefficient computation. Wang and Cheng [316] suggested a fuzzy clustering based on the aggregate attribute method (AAM) for breast cancer detection. To achieve the decision rules from the breast cancer database, Chen and Hsu [317] used the GA-based approach. Şahan, Polat, Kodaz and Güneş [318] hybridized a fuzzy-artificial immune system (FAIS) with the algorithm of KNN. Based on the KNN, neural fuzzy and quadratic classifier (QC) algorithms, researchers developed WBCD classifier models [319]. Furthermore, NF ensemble (NFE), QC ensemble (QCE) and KNN ensemble (KNNE)-based models were also presented.

Lekkas and Mikhailov [320] recommended architecture for evolvable fuzzy rule-based classifiers to be implemented for breast cancer detection. On the basis of association rules (ARs) and neural network, Karabatak and Ince [321] proposed an expert system to classify the breast cancer types. Fuzzy robust principal component analysis (FRPCA) algorithms were used by Luukka [322] for data pre-processing. Then, the classification was made by the similarity classifier (SC). A hybrid hidden Markov model (HMM) fuzzy approach was also proposed for WBCD classification [323]. Based on fuzzy entropy measures (FEMs), Luukka [324] presented a feature selection method in combination with the SC for the application of interest.

Ramathilagam and Huang [325] developed an extended Gaussian version of FCM for the classification task. Vannucci and Colla [326] proposed a model, called LASCUS, based on the FIS and SOM. Fuzzy neural networks, namely fuzzy Gaussian potential neural network (FGPNN) and hierarchical fuzzy neural network (HFNN), were investigated to categorize the database of breast

cancer [327]. The used training procedures were GD and EKF. Jaganathan and Kuppuchamy [328] presented a feature selection method based on a threshold fuzzy entropy (FE). For feature selection, three different criteria were employed: mean selection strategy (MSS), half selection strategy (HSS) and neural network for threshold selection (NNTS). Further to the hyper-rectangular composite neural network (HRCNN) model, a PSO-based fuzzy HRCNN model was also developed in another study [329] for the WBCD problem. Though using the theoretical concept of a fuzzy-rough nearest neighbor (FRNN) algorithm, a classification model was developed by Onan [330].

Fuzzy-based models namely linguistic hedges neuro-fuzzy classifier with selected features (LHNFCSF), conjugate gradient neuro-fuzzy classifier (CGNFC), an adaptive neuro-fuzzy classifier with the linguistic hedges (ANFCLH) and speeding up scaled conjugate gradient neuro-fuzzy classifier (SSCGNFC) were utilized by Azar and El-Said [331] to develop breast cancer classifiers. A hybrid classification system consisting of the CART, RF and/or fuzzy min-max (FMM) neural network was proposed by Seera and Lim [332]. In a BC classification study by Panda and Abraham [333], the ant colony optimization (ACO), PSO, SVM, RF, fuzzy rough KNN (FRKNN) and synthetic minority over-sampling technique (SMOTE) approaches were used. For WBCD classification, there several classification models in a published work on the basis of fuzzy ARTMAP (FARTMAP), fuzzy SAM (FSAM), GA-FSAM, ANFIS, P-ANN and SVM [334]. In another work, researchers employed the wavelet transformation and interval type-2 fuzzy logic system (T2FLS) for data classification [335]. Authors also used Karnik–Mendel iterative procedure (KMIP) and Greenfield–Chiclana Collapsing Defuzzifier (GCCD) algorithm. Hassani and Jafarian [336] evaluated the ability of hybrid methods such as harmony search fuzzy-ART, GA fuzzy-ART, and PSO fuzzy-ART in classifying the datasets of breast cancer. Satishkumar, Sita Mahalakshmi and Katneni [337] proposed a rule discovery algorithm on the basis of swarm intelligence for the breast cancer classification.

Recently, Pota, Esposito and De Pietro [338] presented several rule-based fuzzy systems for classifying the medical databases like WBCD. Recently, another research paper was published on

the use of fuzzy SVM-RWTS AIRS (FSRAIRS) and AIRS techniques for the classification of WBCD [339]. In a study done by Pourpanah et l. [340], brain storm optimization (BSO) is used for the classification of the WBCD. Furthermore, a hybrid model was built by combining BSO with FARTMAP. Hancer [341] presented a fuzzy kernel filter criterion by combining the fuzzy and kernel mutual information estimators for the application of interest.

2.4.5 Other Models

Quinlan [342] used a divide-and-conquer approach of the C4.5 decision tree classifier for WBCD classification. He presented two classification models based on C4.5 and modified C4.5 in a research study [343], a learning technique that combines the classical perceptron algorithm (PA) with the logarithmic simulated annealing (LSA) is implemented to categorize the breast cancer database. In addition to the C4.5 decision tree, Smith and Bull [344] employed the genetic algorithm and programming (GAP) for analysis of the WBCD. Bagui, Bagui, Pal and Pal [345] compared the results of the k-rank nearest neighbour (KRNN) with the conventional KNN. Using a Bayesian feature selection (BFS) method, a classification model was proposed for classifying the breast cancer data [346]. In another study [347], the Bayesian networks were utilized for imputation in the breast cancer classification.

The kernel principal component analysis (KPCA) on the BC database was performed by Hoffmann [348]. The KPCA was then compared with PCA, SVM and Parzen density. The FS-AIRS methodology is another approach that was proposed in the literature for WBCD classification [349]. Using the ordered weighted averaging (OWA) operator, Cheng, Wang and Wu [350] introduced a classifier for this database. Mohammed, Naugler and Far [351] applied OWA-based methods employing KNN, Laplace and logistic regression (LLR) and SVM to the problem of breast cancer detection. The variable predictive model based class discrimination (VPMCD) and discriminating partial correlation coefficient metric (DPCCM) machine learning approaches were used in the

literature [352] for the classification of BC. Furthermore, LDA, CART and TreeNet methods were used as a basis for comparison.

Several classification models were developed by Lavanya and Rani [353] for breast cancer classification. The best model was obtained using the principal components attribute evaluation (PCAE) FS method. Other FS methods were CFS subset evaluation (CFSSE), Chi-squared attribute evaluation (CSAE), classifier subset evaluation (CSE), consistency subset evaluation (COSE), filtered attribute evaluation (FAE), filtered subset evaluation (FSE), gain ratio attribute evaluation (GRAE), information gain attribute evaluation (IGAE), relief attribute evaluation (RAE), SVM attribute evaluation (SVMAE), symmetric uncertainty attribute evaluation (SUAE) and symmetric uncertainty attribute set evaluation (SUASE). Malar and Nadarajan [354] developed different classification models based on the DT, SVM, isotonic separation (IS), and evolutionary IS (EIS) methods. The EIS method used GA for the training phase. Using the cluster analysis methods with feature selection, a hybrid model was suggested by Chen [355] to analyze the WBCD database. Combining the RST and KNN classifier, El-Baz [356] investigated the breast cancer database in terms of screening and categorization. To achieve a reliable method for the breast cancer detection, Onan [357] developed ensembles of bagging, AdaBoost, dagging, multi boost, random sunspace, and decorate in conjunction with the SVM, MLP, LMT, RF, Bayes Net, KNNs, FURIA, C4.5, KR, kernel logistic regression (KLR), RIPPER, KStar, NB, and simple CART. Karabatak [358] introduced another NB and weighted NB (W-NN) classifiers to detect the BC type. In another published research [359], the BC classification ability of SMO, C4.5, decorate, NB, bagging, and IBK algorithms was examined and compared.

Rashmi, Lekha and Bawane [360] implemented the KNN algorithm for the classification of the BC datasets. Modi and Ghanchi [361] investigated several classification and feature selection methods and machine learning algorithms, including NB, C4.5, RF, Bayes net (BN) and KNN to classify the breast cancer datasets. Sheikhpour, Sarram and Sheikhpour [362] developed several kernel density estimation (KDE)-based classifiers for various breast cancer cases. They used the PSO and GA

algorithms for the feature selection and bandwidth determination of the classifiers. For the problem of breast cancer classification, Azar, Inbarani and Renuga Devi [363] developed several classifiers using several methods such as Zero R, decision table, C4.5, random tree (RT), RF, MLP-ANN, IBk, KStar, LWL, NB, KNN, classical RST and improved dominance-based rough set (IDRSA). Sayed, Darwish, Hassanien and Pan [364] compared the breast cancer classification ability of whale optimization algorithm (WOA) to that of GA, PCA, statistical dependency, mutual information (MI), random subset feature selection (RSFS), sequential forward selection (SFS), and sequential floating forward selection (SFFS). Dora, Agrawal, Panda and Abraham [365] implemented the Gauss-Newton representation-based algorithm (GNRBA) on the cancer databases. The GNRBA model then was compared to other models like BP-ANN, Koza's model (KM) and GO-ANN.

Lu et al. [366] developed a genetic algorithm-based online gradient boosting (GAOGB) classifier. They also implemented other methods like online gradient boosting with the adaptive linear regressor (OLRGB), online adaptive boosting with the adaptive linear regressor (OLRAB), online sequential extreme learning machine (OSELM) and online linear regressor (OLR). With the aim of efficient dimensionality reduction, Hu et al. [367] applied ELM-SOM+ technique to the WBCD. Mohamed et al. [368] compared the classification performance of the Parasitism-Predation algorithm (PPA) to that of Cuckoo search (CS), cat swarm optimization (CSO) and crow search algorithm (CSA). Alroobaea et al. [369] developed several Bayesian-based models, including Gaussian distribution (GDis), Generalized Gaussian distribution (GGDis), Bounded Gaussian distribution and Bounded generalized Gaussian distribution (BGGDis) in conjunction with Bayesian inference (B) or maximum likelihood (ML). Mushtaq [370] presented several KNN-based models for breast cancer classification.

In 2020, Devarria et al. [371] proposed two frameworks, namely D score and F2 score in combination with the GP algorithm and to classify between malignant and benign cases. In another study, Hancer [372] employed the WBCD for multi-objective clustering. Nayak et al. [373] implemented a Filter Approach using Elitism based Multi-objective Differential Evolution for

feature selection (FAEMODE) and compared the results to the outputs of methods based on SFS and SBS. Employing several datasets, including the WBCD, Aydemir [374] applied the Polygon Area Metric method to evaluate the performance of classifiers. In another study, Habib et al. [375] employed multi-objective particle swarm optimization (MOPSO), multi-objective evolutionary algorithm based on decomposition (MOEA/D) and non-dominated sorting genetic algorithm (NSGA-II).

2.5 ANALYSIS OF THE LITERATURE MODELS

2.5.1 Assessment Parameters

To evaluate the performance of the created models for classification purposes, the following parameters are commonly determined: classification accuracy, sensitivity and specificity. Eqs (2.1) to (2.3) mathematically represent these parameters in a respective order.

$$Accuracy\% = \frac{tn + tp}{tp + fp + fn + tn} \times 100 \qquad (2.1)$$

$$Sensitivity\% = \frac{tp}{tp + fn} \times 100 \qquad (2.2)$$

$$Specificity\% = \frac{tn}{tn + fp} \times 100 \qquad (2.3)$$

where *tn*, *tp*, *fp*, and *fn* denote the true negative, true positive, false positive, and false negative, respectively.

2.5.2 Evaluation of the WBCD Models

Table 2.2 gives the error analysis results of the presented neural-based models in the literature for WBCD classification. **Fig. 2.9** demonstrates the histogram of the literature ANN-based models'

accuracy for WBCD classification. As can be observed from this figure, most of the published ANN-based models provide accuracies more than 95%. However, some developed models have very low accuracy. According to **Table 2.2**, these models were presented by Janghel et al. [260]. Other models with accuracies less than 90% are BGD-ANN [257], BGDM-ANN [257], SOM [274] and MLP-ANN [274].

Table 2.2: Performance of the available neural-based WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
FF-ANN (all features) [248]	1997	96.8	*	*
FF-ANN (selected features) [248]	1997	98.6	*	*
FF-ANN [249]	1996	96.5	*	*
PFF-ANN (rule#1) [247]	1996	95.4	*	*
PFF-ANN (rule#2) [247]	1996	94.7	*	*
PFF-ANN (rule#3) [247]	1996	97.1	*	*
PFF-ANN (rule#1, pre-processed data) [251]	2000	97.4	*	*
PFF-ANN (rule#2, pre-processed data) [251]	2000	98.1	*	*
PFF-ANN (rule#3, pre-processed data) [251]	2000	98.2	*	*
Binarized ANN [252]	1997	95.2	*	*
Normalized ANN [252]	1997	95.8	*	*
Continuous ANN [252]	1997	97.4	*	*
MLP-ANN [253]	2000	95.7	91.3	98.1
MOE-ANN [253]	2000	96.3	93.7	97.7
RBF-ANN [253]	2000	97.0	97.0	97.1
GR-ANN [253]	2000	96.8	94.6	98.0
GDX-ANN [254]	2007	97.7	*	*
Linear-ANN [254]	2007	96.0	*	*
AM-MLP [256]	2013	99.3	100	97.9
BP-ANN [256]	2013	94.5	87.4	98.3
BGD-ANN [257]	2011	83.3	*	*
QN-ANN [257]	2011	98.4	*	*
BGDM-ANN [257]	2011	84.4	*	*
RBP-ANN [257]	2011	98.6	*	*
LM-ANN [257]	2011	99.3	*	*
CG-AMM [257]	2011	99.0	*	*
BP-ANN [258]	2017	98.0	*	*
BP-ANN [259]	**1996**	**96.7**	*	*
LVQ [259]	**1996**	**96.6**	*	*
LVQ [261]	2002	96.7	*	*
BLVQ [261]	2002	96.8	*	*
BP-ANN [260]	2010	51.9	17.4	79.5
RBF-ANN [260]	2010	49.8	19.6	74.2

**indicates that the value of the parameter in not reported in the original work*

Table 2.2: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
LVQ [260]	2010	95.8	95.8	95.8
P-ANN [260]	2010	49.8	19.6	74.2
R-ANN [260]	2010	52.7	21.0	75.5
CL-ANN [260]	2010	74.5	25.0	77.1
GA-ART-ANN [263]	2007	97.6	*	*
BP-ANN [264]	2010	98.2	*	*
GA-W-ANN [264]	2010	98.6	*	*
GA-MOO-ANN [264]	2012	98.9	98.5	99.1
RLS-LLW-ANN [20]	2011	97.3	*	*
KF-RBF-ANN [20]	2011	96.4	*	*
RLS-RBF-ANN [20]	2011	97.1	*	*
ANN [21]	2015	95.0	96.3	92.7
GA-RP-ANN [22]	2014	99.4	99.5	97.6
GA-LM-ANN [22]	2014	98.9	97.8	98.0
GA-GD-ANN [22]	2014	99.4	98.5	97.1
ICA-MLP-ANN [270]	2013	97.8	*	*
PSO-MLP-ANN [270]	2013	97.6	*	*
BP-ANN [271]	2016	91.2	88.9	93.8
DE-BP- ANN [271]	2016	92.6	91.4	93.9
PSO-BP- ANN [271]	2016	95.6	94.3	97.0
KPS-RBF-ANN [272]	2012	97.9	*	*
EKF-RBF-ANN [272]	2012	96.4	*	*
MP-ANN [273]	2002	98.1	*	*
SOM [274]	2011	86.5	81.3	89.4
MLP-ANN [274]	2011	87.5	91.75	95.0
PNCF [274]	2011	96.0	99.0	90.0
PNSCF [274]	2011	97.9	98.5	94.3
RF-PCA-ANN [275]	2013	98.0	*	*
PSO-ANN [275]	2013	97.4	*	*
SBSP-ANN [276]	2013	98.6	*	*
BP-ANN (average) [277]	2015	91.2	95.3	82.8
GO-ANN (average) [277]	2015	98.8	99.1	98.4
RST-BP-ANN [278]	2015	98.6	98.8	98.6
AM-MLP-ANN [279]	2015	97.9	98.9	96.9
ANN [280]	2015	95.3	97.6	97.2
AR-ANN [280]	2015	94.1	93.7	96.1
C-ANN [280]	2015	95.9	98.5	97.5
GA-ANN [280]	2015	94.7	97.1	96.1
BPSS-BP-ANN [281]	2016	95.3	*	*
CG-RIW-BP-ANN [282]	2016	98.9	100	98.2
LM-RIW-BP-ANN [282]	2016	99.0	99.1	99.0
CG-DBN-BP-ANN [282]	2016	99.6	100	99.4
LM-DBN-BP-ANN [282]	2016	99.7	100	99.5
NSGA-II-BP-ANN [283]	2018	97.7	97.6	97.1
RBF-ANN [288]	2009	96.6	97.3	96.5
FF-ANN [295]	2015	96.2	*	*

Table 2.2: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
MLP-ANN [294]	2007	91.9	91.2	92.3
R-ANN [294]	2007	98.6	98.1	98.9
C-ANN [294]	2007	97.5	96.9	97.8
P-ANN [294]	2007	98.2	98.1	98.9
ANN [299]	2014	92.4	93.0	92.0
MLP-ANN [301]	2017	96.7	*	*
RBF-ANN [301]	2017	95.8	*	*
GA-MLP-ANN [301]	2017	98.5	*	*
GA-RBF-ANN [301]	2017	98.4	*	*
MLP-ANN [309]	1999	94.8	*	*
MLP-ANN [321]	2009	95.2	*	*
P-ANN [334]	2015	93.9	*	*
PCA-P-ANN [334]	2015	94.9	*	*
Wavelets-P-ANN [334]	2015	93.8	*	*
MLP-ANN [363]	2017	95.1	*	*
BP-ANN [363]	2017	95.1	*	*
BP-ANN (average) [365]	2017	91.2	*	*
GO-ANN (average) [365]	2017	98.8	*	*
MLP [304]	2019	96.7	97.1	96.4
RBF [304]	2019	95.4	93.4	96.5
MLP-boosting [304]	2019	98.1	97.8	99.8
RBF-boosting [304]	2019	96.4	94.4	97.5
DFNN-PSO [284]	2020	*	97.9	*
DFNN-MTO [284]	2020	*	100	*
DFNN-MTOCL [284]	2020	*	97.9	*
ANN [285]	2020	99.4	99.9	98.4

Statistical parameters values of the studied SVM-based classifiers for the WBCD problem are given in **Table 2.3**. In accordance with **Table 2.3**, more than 70% of the investigated SVM-based models for the application of interest provided accuracies more than 95%. On the other hand, three models, including the SVM (quadratic) [299], SVM (linear) [299] and SVM [281] showed accuracies less than 90%.

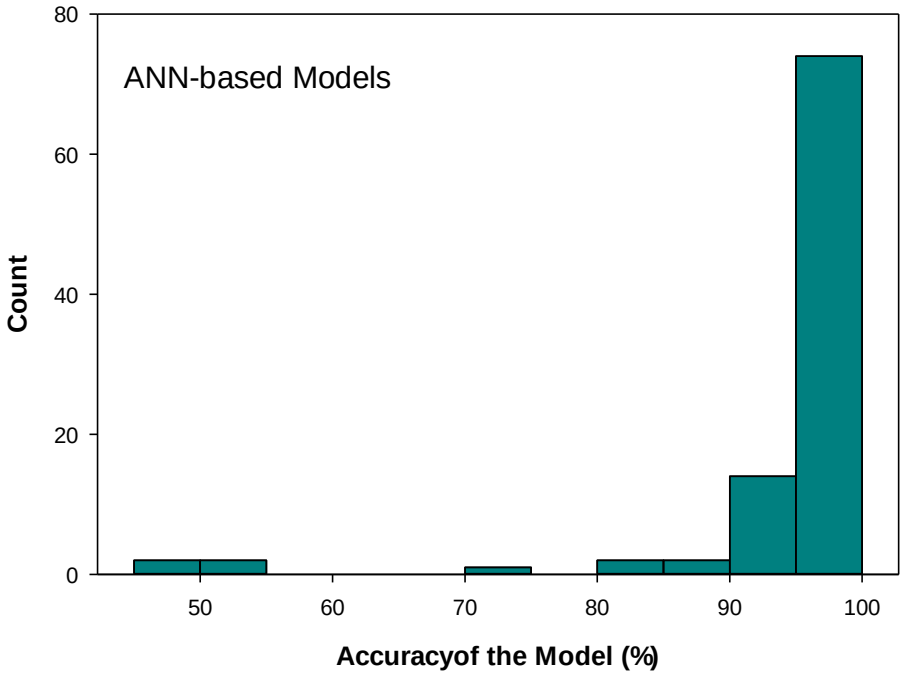


Fig. 2.9: Histogram of the accuracies obtained from the developed ANN-based models in the literature

Table 2.3: Performance of the available SVM-based WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
SVM [281]	2016	83.0	*.	*
SVM [286]	1998	97.2	*.	*
GTO-SVM [286]	1998	96.6	*.	*
LS-SVM (average) [287]	2007	96.5	95.8	97.3
SVM [288]	2009	92.1	86.7	95.9
FS-SVM [289]	2009	99.51	99.6	97.7
FS-SVM [290]	2013	95.6	97.0	95.0
KFS-SVM [290]	2013	97.0	97.0	96.0
RS-SVM (average) [291]	2011	96.7	99.9	100
SVM [292]	2013	96.5	*	*
CC-SVM (pedagogical) [292]	2013	97.1	*	*
CC-SVM (decompositional) [292]	2013	95.9	*	*
SVM [293]	2014	97.1	*	*
SVM (RBF) [294]	2007	99.5	99.4	99.6
SVM (linear) [295]	2015	97.9	*	*
SVM (quadratic) [295]	2015	97.3	*	*
SVM (polynomil) [295]	2015	97.5	*	*

**indicates that the value of the parameter in not reported in the original work*

Table 2.3: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
SVM (RBF) [295]	2015	98.0	*	*
SVM (MLP) [295]	2015	96.7	*	*
FS-SVM [296]	2012	97.0	95.2	97.8
PSO-SVM [296]	2012	99.3	99.5	99.1
SVM (exponential-Gaussian) [297]	2012	98.3	99.4	94.4
K-SVM [298]	2014	97.4	*	*
SVM (RBF) [299]	2014	93.6	94.0	92.0
SVM (linear) [299]	2014	78.5	72.0	81.0
SVM (quadratic) [299]	2014	72.9	68.0	75.0
SVM [300]	2014	93.7	99.2	86.5
SVM [301]	2017	96.8	*	*
GA-SVM [301]	2017	99.0	*	*
SMOTE-SVM (average) [333]	2014	96.4	*	*
FRSE-PSO-SVM (average) [333]	2014	96.4	*	*
SVM [334]	2015	93.9	*	*
PCA-SVM [334]	2015	94.9	*	*
Wavelets-SVM [334]	2015	93.8	*	*
OWA-SVM [351]	2016	96.3	*	*
SVMAE[353]	2011	94.6	*	*
SVM [354]	2013	96.6	96.5	96.8
BK-SVM [302]	2019	97.5	*	*
Bagging (SVM/CART) [302]	2019	98.5	*	*
AdaBoost (SVM/CART) [302]	2019	98.1	*	*
WMV (SVM/CART) [302]	2019	98.5	*	*
NB (SVM/CART) [302]	2019	98.3	*	*
EVEN (SVM/CART) [302]	2019	98.5	*	*
MDM (SVM/CART) [302]	2019	98.5	*	*
SCANN (SVM/CART) [302]	2019	98.5	*	*
TrEnL (SVM/CART) [302]	2019	98.2	*	*
SVM [304]	2019	97.1	95.5	98.0
polynomial-SVM [304]	2019	98.4	98.7	98.3
CPG-SVM (average) [304]	2019	99.7	99.5	99.4
CWV-BANN-SVM [304]	2019	100	100	100
SVM [374]	2020	98.0	100	95.0

Histogram of the accuracy of the SVM-based models presented for WBCD is depicted in **Fig. 2.10**. With accuracy, sensitivity and specificity of 100%, the CWV-BANN-SVM model [304] is the best literature model for the classification of the WBCD. Looking at other effective SVM-based models for BC classification, it can be observed that hybrid of SVM with other techniques is a great way to improve the classification performance of the final model for the WBCD.

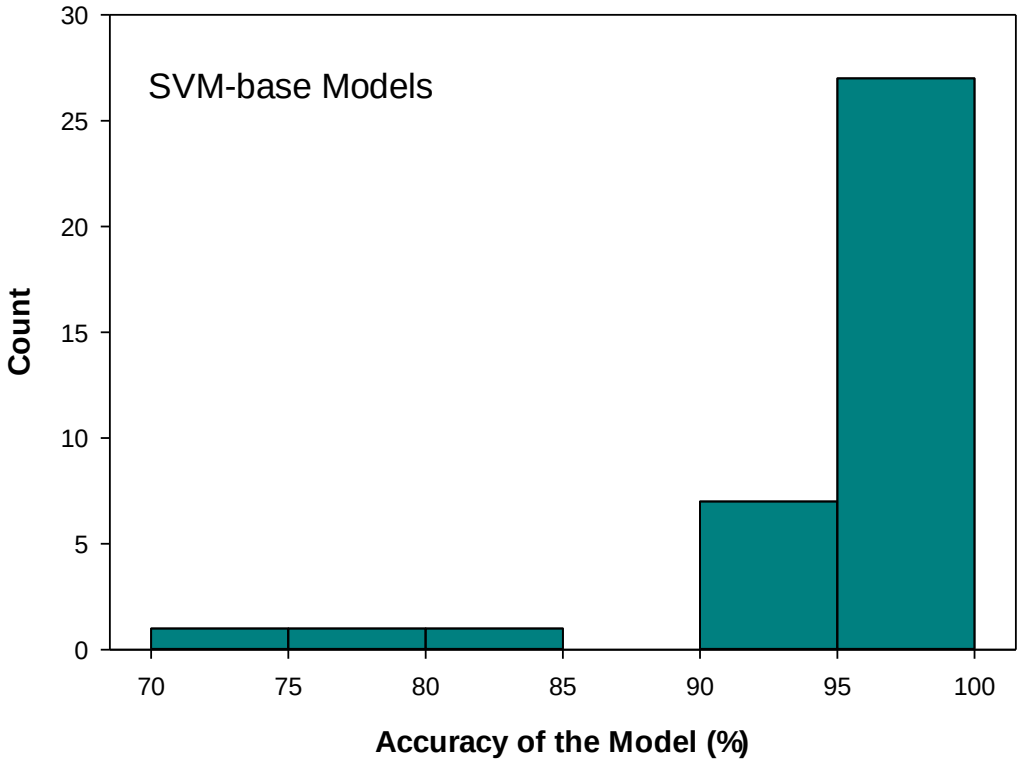


Fig. 2.10: Histogram of the accuracies obtained from the developed SVM-based models in the literature

For the literature rule/fuzzy-based models, the error analysis results are tabulated in **Table 2.4**. the majority of these classifiers provide satisfactory outcomes. However, nine models out of 82 studied rule/fuzzy-based literature models have accuracies below 95%. Histogram of the rule/fuzzy-based models' accuracy is demonstrated in **Fig. 2.11**. As given in **Table 2.4**, a fuzzy-based model, namely FSRAIRS [339], provided the best achievable accuracy, i.e. 100%. However, since there is no information regarding the sensitivity and specificity values of this model and some other models as well, it is not possible to conclude that this model presents the best results for the WBCD problem. Similar to SVM-based models, hybrid of fuzzy models with some algorithms provided satisfactory results.

Table 2.4: Performance of the rule/fuzzy-based WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
RIAC [305]	1996	95.0	*	*
GA-FL (two-rule) [306]	1998	96.7	*.	*
GA-FL (single-rule) [306]	1998	96.4	*	*
GA-FL (single-rule) [307]	1999	97.1	*	*
GA-FL (two-rule) [307]	1999	97.4	*	*
GA-FL (three-rule) [307]	1999	97.8	*	*
GA-FL (four-rule) [307]	1999	97.8	*	*
GA-FL (five-rule) [307]	1999	97.5	*	*
GP-FL [308]	1999	95.0	*	*
NEFCLASS [309]	1999	95.1	*	*
FEBFC [310]	2001	94.7	*	*
FEBFC (with feature selection) [310]	2001	95.1	*	*
SSV (3 crisp rules) [311]	2001	96.5	*	*
FSM (12 fuzzy rules) [311]	2001	96.3	*	*
C-MLP2LN (average) [311]	2001	97.2	*	*
GG-FL (average) [312]	2003	94.1	*	*
FuzzyQSBA [313]	2004	92.2	*	*
WSBA [313]	2004	92.8	*	*
IRSS [314]	2004	95.9	*	*
ANFIS [315]	2005	95.9	*	*
GA-ANFIS [315]	2005	97.7	*	*
DT-ANFIS [315]	2005	98.0	*	*
CC-ANFIS [315]	2005	97.4	*	*
AAM-FL [316]	2006	98.2	*	*
GA-Rule [317]	2006	96.6	*	*
FAIS-KNN [318]	2007	99.1	*	*
NF [319]	2012	94.3	*	*
NFE [319]	2012	96.6	*	*
NF-KNN-QC [319]	2012	97.1	*	*
eClass [320]	2009	99.5	*	*
FS-eClass [320]	2009	99.5	*	*
AR1-ANN [321]	2009	97.4	*	*
AR2-ANN [321]	2009	95.6	*	*
FRPCA1 [322]	2009	98.2	*	*
FRPCA2 [322]	2009	98.1	*	*
FRPCA3 [322]	2009	98.2	*	*
SC-FEM1 [324]	2011	97.1	*	*
SC-FEM2 [324]	2011	97.2	*	*
LASCUS [326]	2011	98.0	*	*
GD-FGPNN [327]	2012	98.1	98.0	98.1
EKF-FGPNN [327]	2012	98.2	98.3	98.1
GD-HFNN [327]	2012	98.1	98.0	98.1
EKF-HFNN [327]	2012	98.2	98.3	98.1
GD-FNN [327]	2012	98.2	98.3	97.8
EKF-FNN [327]	2012	97.8	97.2	98.3

**indicates that the value of the parameter in not reported in the original work*

Table 2.4: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
NNTS-FE [328]	2013	97.3	94.0	99.0
MSS-FE [328]	2013	96.0	93.0	97.0
HSS-FE [328]	2013	96.7	94.0	98.0
HRCNN [329]	2014	95.0	*	*
PSO-HRCNN [329]	2014	97.8	*	*
FRNN [330]	2015	99.7	*	*
LHNFCSF [331]	2013	98.9	*	*
ANFCLH [331]	2013	97.5	*	*
SSCGNFC [331]	2013	97.5	*	*
SCGNFC [331]	2013	97.8	*	*
FMM (average) [332]	2014	95.2	*	*
CART-FMM (average) [332]	2014	94.6	*	*
CART-RF-FMM (average) [332]	2014	97.9	*	*
FRSE-ACO-FRKNN (average) [333]	2014	95.6	*	*
FRSE-PSO-FRNN (average) [333]	2014	95.6	*	*
SMOTE-FRNN (average) [333]	2014	98.0	*	*
FARTMAP [334]	2015	94.9	*	*
PCA-FARTMAP [334]	2015	96.3	*	*
Wavelets-FARTMAP [334]	2015	95.6	*	*
ANFIS [334]	2015	93.1	*	*
PCA-ANFIS [334]	2015	95.5	*	*
Wavelets-ANFIS [334]	2015	95.7	*	*
FSAM [334]	2015	94.9	*	*
PCA-FSAM [334]	2015	95.3	*	*
Wavelets-FSAM [334]	2015	96.2	*	*
GA-FSAM [334]	2015	95.6	*	*
GA-PCA-FSAM [334]	2015	95.9	*	*
GA-Wavelets-FSAM [334]	2015	97.4	*	*
IT2FLS-KMIP [335]	2015	95.8	*	*
PCA-IT2FLS-KMIP [335]	2015	96.3	*	*
Wavelets-IT2FLS-KMIP [335]	2015	97.8	*	*
IT2FLS-GCCD [335]	2015	96.9	*	*
PCA-IT2FLS-GCCD [335]	2015	96.9	*	*
Wavelets-IT2FLS-GCCD [335]	2015	97.9	*	*
FL [338]	2017	97.6	*	*
FSRAIRS [339]	2015	100	*	*
AIRS (average) [339]	2015	96.9	*	*
FARTMAP [340]	2019	96.0	*	*
FARTMAP-BSO (best) [340]	2019	96.7	*	*

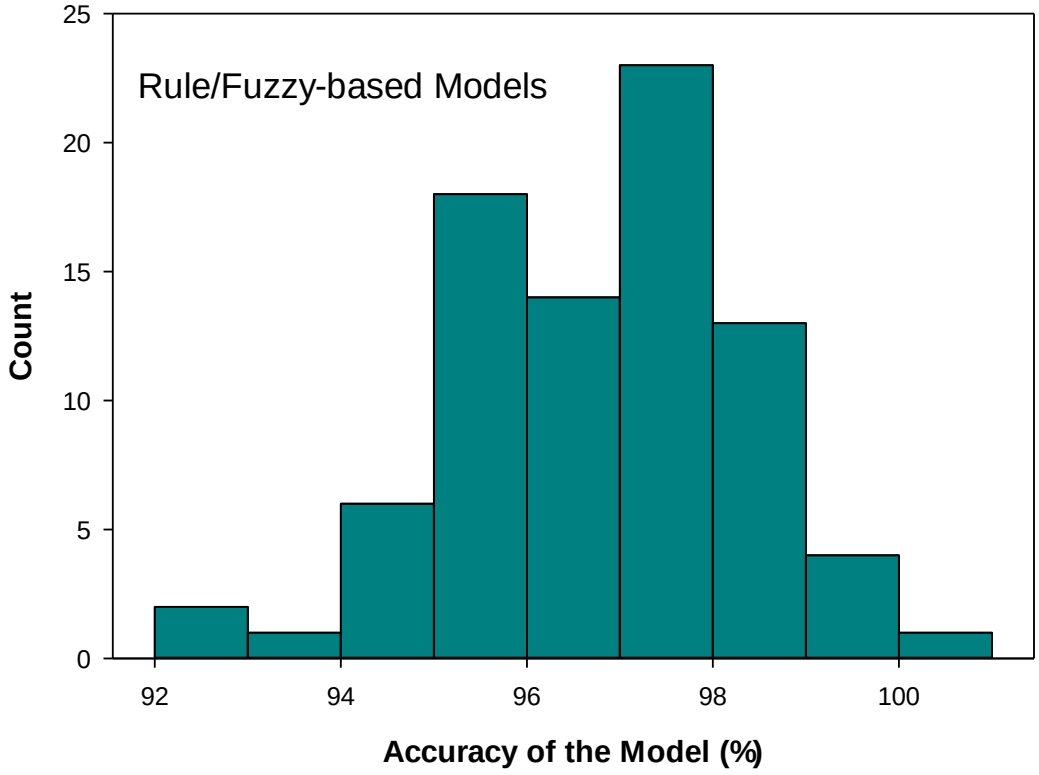


Fig. 2.11: Histogram of the accuracies obtained from the developed rule/fuzzy-based models in the literature

Table 2.5 presents the overall performance of the developed WBCD classifiers based on the decision trees. The histogram graph for the accuracies of the tree-based models is shown in **Fig. 2.12**. According to the error analysis presented in **Table 2.5** and **Fig. 2.12**, more than half of the available tree-based classifiers can be used for the WBCD problem with accuracies more than 95%. Except for a model called DT-AdaBoost [315], other models predict the breast cancer class with accuracies higher than 90%.

Table 2.6 presents the error analysis for KNN-based models. Histogram of the accuracies of the reviewed KNN-based models is shown in **Fig. 2.13**. As can be seen, most developed KNN models provided results with accuracies higher than 95%. Furthermore, it can be observed that hybrid

models like RST-KNN [356] and KNN-Chi2 [370] reproduced the targets with satisfactory accuracy, sensitivity and specificity.

Table 2.5: Performance of the available tree-based WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
C4.5 [249]	1996	95.8	*.	*
CART [259]	1996	94.2	*.	*
C4.5 [21]	2015	94.3	96.2	91.1
C4.5 [286]	1998	93.4	*	*
RF (10 trees) [299]	2014	90.1	92.0	89.0
RF (100 trees) [299]	2014	95.6	97.0	94.0
IG-DT [300]	2014	95.6	93.7	93.7
Gini-DT [300]	2014	94.0	90.0	92.7
C4.5 [301]	2017	94.0	*	*
GA-C4.5 [301]	2017	93.2	*	*
DT-AdaBoost [315]	2005	61.0	*	*
GA-RF [301]	2017	95.3	*	*
C4.5 [309]	1999	95.1	*	*
C4.5 [342]	1996	94.7	*	*
Modified-C4.5 [342]	1996	94.7	*	*
C4.5 [305]	1996	96.0	*	*
FRSE-PSO-RF (average) [333]	2014	97.3	*	*
SMOTE-RF (average) [333]	2014	97.4	*	*
C4.5 [344]	2003	94.4	*	*
CART [352]	2009	98.7	*	*
TreeNet [352]	2009	98.4	*	*
DT [354]	2013	92.4	93.0	93.4
C4.5 [359]	2015	94.6	94.6	95.6
SMO-C4.5-NB-Decorate [359]	2015	97.0	96.3	97.4
SMO-C4.5-NB-IBK [359]	2015	97.3	97.5	97.2
SMO-C4.5-Bagging-NB [359]	2015	96.9	97.1	96.7
RF [301]	2017	95.4	*	*
C4.5 [361]	2016	94.6	*	*
C4.5-KNN-BN [361]	2016	95.3	*	*
C4.5-BN [361]	2016	94.9	*	*
C4.5-NB [361]	2016	97.0	*	*
C4.5-RF [361]	2016	95.7	*	*
RF [361]	2016	96.9	*	*
C4.5 [363]	2017	94.2	*	*
RF [363]	2017	95.4	*	*

**indicates that the value of the parameter in not reported in the original work*

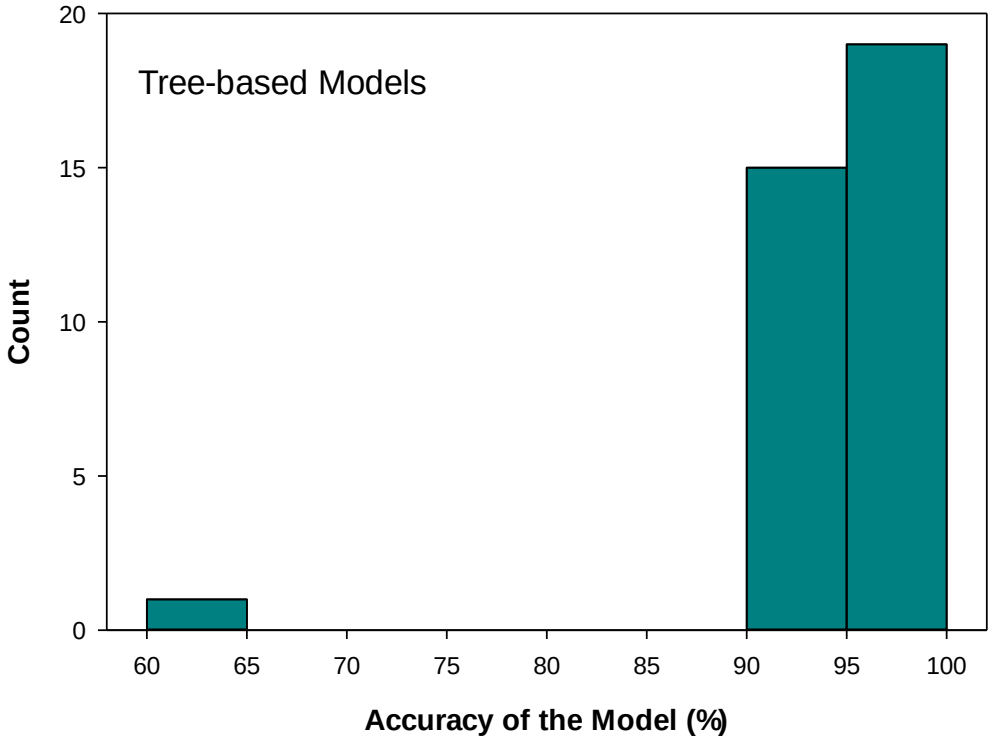


Fig. 2.12: Histogram of the accuracies obtained from the developed tree-based models in the literature

Table 2.6: Performance of the available KNN-based WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
KNN [259]	1996	96.6	*	*
KNN [281]	2016	90.6	*	*
KNN [319]	2012	96.4	*	*
KNN (average) [345]	2003	96.4	*	*
OWA-KNN [351]	2016	99.7	*	*
KNN [356]	2015	98.8	98.8	98.9
RST-KNN [356]	2015	99.4	100	99.2
KNNE [319]	2012	96.4	*	*
KNN [360]	2016	85.6	*	*
KNN [363]	2017	93.5	*	*
KNN [374]	2020	98.0	99.0	95.0
KNN (best model) [370]	2019	96.6	98.2	96.3
KNN-LSVC (best model) [370]	2019	97.7	99.0	98.4
KNN-Chi2 (best model) [370]	2019	99.4	99.1	100

**indicates that the value of the parameter in not reported in the original work*

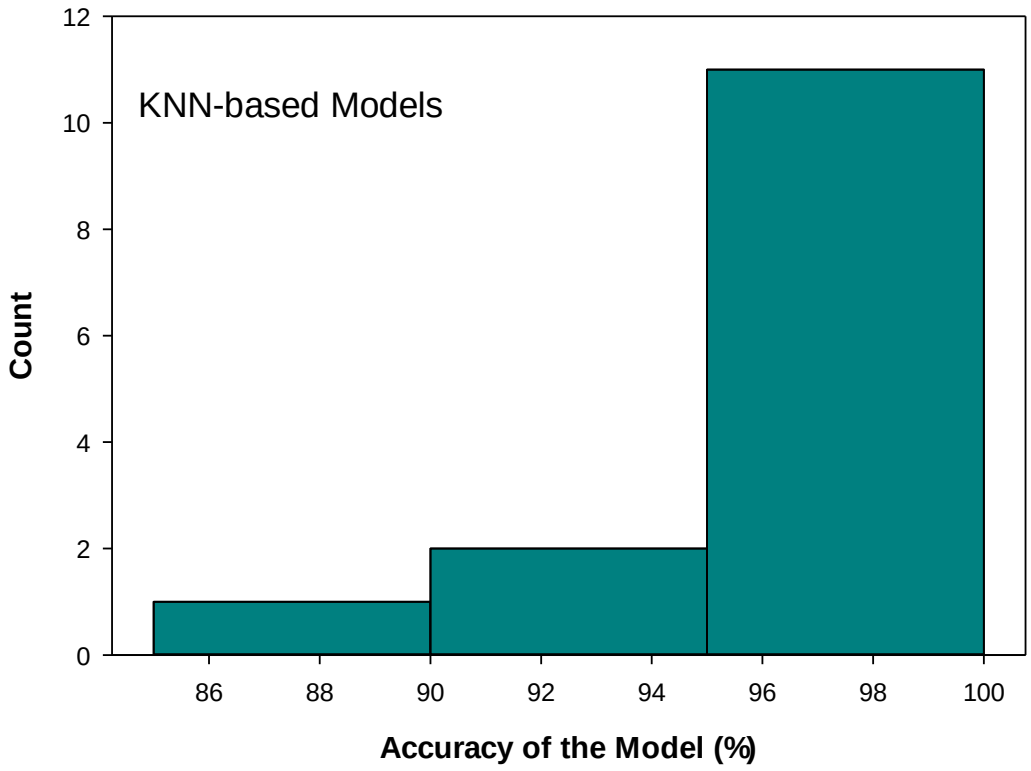


Fig. 2.13: Histogram of the accuracies obtained from the developed KNN-based models in the literature

Similar to the ANN-based, SVM-based, rule/fuzzy-based, tree-based and KNN-based models, the error analysis for other available WBCD classification models, reviewed in this study, is collected and given in **Table 2.7**.

The accuracy histogram for these classifiers is depicted in **Fig. 2.14**. With accuracies less than 75%, nine models including QDA [259], MBL [300], AdaBoost [315], GA-AdaBoost [315], CC-AdaBoost [315], NB , Zero R [363], TGC [24], CGCRM [24] are amongst the weakest developed models in the literature. On the other hand, GNRBA [365], RST-KNN [356], RotationF [301], GA-RotationF [301], OWA-KNN [351] provide accuracies more than 99% for classifying the WBCD.

Table 2.7: Performance of the other available WBCD classification models in the literature

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
LFC [259]	1996	94.4	*	*
LDA [259]	1996	96.0	*	*
QDA [259]	1996	34.5	*	*
ASR [259]	1996	94.7	*	*
ASI [259]	1996	95.6	*	*
SNB [259]	1996	96.6	*	*
NB [259]	1996	96.4	*	*
AIRS [261]	2002	97.2	*	*
LR [21]	2015	94.3	97.2	94.8
GA [21]	2015	98.8	100	98.0
CGCRMM [24]	2013	72.0	*	*
TGC [24]	2013	70.0	*	*
k-means [274]	2011	89.9	94.2	85.5
NB [281]	2016	88.7	*	*
OC1 [286]	1998	95.9	*	*
OTG [286]	1998	95.7	*	*
NB [299]	2014	65.3	57.0	72.0
NB [300]	2014	96.7	99.6	92.0
MBL [300]	2014	63.1	45.7	36.6
Ensemble [300]	2014	97.4	97.9	95.1
LR [301]	2017	98.5	*	*
BN [301]	2017	95.3	*	*
RotationF [301]	2017	99.5	*	*
GA-LR [301]	2017	98.4	*	*
GA-BN [301]	2017	95.3	*	*
GA-RotationF [301]	2017	99.5	*	*
GG [312]	2003	93.1	*	*
AdaBoost [315]	2005	61.9	*	*
GA-AdaBoost [315]	2005	62.2	*	*
CC-AdaBoost [315]	2005	63.1	*	*
QC [319]	2012	94.5	*	*
QCE [319]	2012	96.6	*	*
PCA [322]	2009	97.7	*	*
SC [324]	2011	97.5	*	*
PA-LSA [343]	2002	98.3	*	*
GAP [344]	2003	95.6	*	*
KRNN (average) [345]	2003	96.2	*	*
BFS [346]	2004	96.5	*	*
FS-AIRS [349]	2005	98.5	*	*
OWA [350]	2009	98.4	*	*
OWA-LLR [351]	2016	95.5	*	*
DPCCM [352]	2009	97.1	*	*
VPMCD [352]	2009	97.1	*	*
LDA [352]	2009	95.7	*	*
PCAE [353]	2011	97.0	*	*

**indicates that the value of the parameter in not reported in the original work*

Table 2.7: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
CFSSE [353]	2011	94.8	*	*
CSAE [353]	2011	94.6	*	*
CSE [353]	2011	95.1	*	*
COSE [353]	2011	95.1	*	*
FAE [353]	2011	94.6	*	*
FSE [353]	2011	94.8	*	*
GRAE [353]	2011	94.4	*	*
IGAE [353]	2011	94.6	*	*
RAE [353]	2011	94.6	*	*
SUAE [353]	2011	94.6	*	*
SUASE [353]	2011	94.0	*	*
IS [354]	2013	97.5	95.4	96.1
EIS [354]	2013	98.6	98.3	97.5
NB [358]	2015	96.2	*	*
W-NB [358]	2015	98.5	99.1	98.3
Decorate [359]	2015	96.4	94.6	96.7
Dagging [359]	2015	96.6	96.2	97.5
IBK [359]	2015	95.1	95.1	96.7
NB [359]	2015	96.0	95.9	95.2
SMO [359]	2015	97.0	96.2	97.3
SMO-Bagging-NB-IBK [359]	2015	97.0	97.1	96.9
BN [361]	2016	97.1	*	*
NB [361]	2016	96.0	*	*
PSO-KDE (average) [362]	2016	97.7	94.0	99.7
GA-KDE (average) [362]	2016	96.9	91.6	99.7
IDRSA [363]	2017	96.5	*	*
RST [363]	2017	95.3	*	*
Zero R [363]	2017	65.5	*	*
NB [363]	2017	95.6	*	*
PSO [363]	2017	95.4	*	*
IBK [363]	2017	93.7	*	*
KSTAR [363]	2017	94.7	*	*
LWL [363]	2017	92.2	*	*
M-Classifier [363]	2017	95.7	*	*
Decision table [363]	2017	93.3	*	*
RT [363]	2017	93.3	*	*
WOA [364]	2017	98.7	*	*
SFFS [364]	2017	92.9	*	*
SFS[364]	2017	89.1	*	*
RSFS [364]	2017	94.4	*	*
MI [364]	2017	93.1	*	*
PCA [364]	2017	92.3	*	*
SD [364]	2017	93.9	*	*
GA [364]	2017	95.9	*	*
KM (average) [365]	2017	92.5	*	*
GNRBA (average) [365]	2017	99.3	*	*

Table 2.7: Continued.

Model	Year	Performance (%)		
		Accuracy	Sensitivity	Specificity
D score-GP (average) [371]	2020	98.9	98.9	98.4
F2 score-GP (average) [371]	2020	99.4	98.7	99.1
SFS [373]	2020	90.1	*	*
SBS [373]	2020	89.9	*	*
FAEMODE [373]	2020	95.3	*	*
GAOGB [366]	2019	94.3	93.1	93.2
OSELM [366]	2019	93.3	89.6	95.6
OLRAB [366]	2019	90.6	91.0	90.6
OLRGB [366]	2019	87.8	86.7	88.6
OLR [366]	2019	66.6	63.3	68.5
PPA (average) [368]	2019	99.4	*	*
CS (average) [368]	2019	99.2	*	*
CSA (average) [368]	2019	99.0	*	*
CSO (average) [368]	2019	99.3	*	*
WOA (average) [368]	2019	99.2	*	*
GDis-ML [369]	2020	88.3	*	*
GGDis-ML [369]	2020	92.3	*	*
BGDis-ML[369]	2020	89.2	*	*
BGGDis-ML[369]	2020	93.2	*	*
GDis-B [369]	2020	89.8	*	*
GGDis-B [369]	2020	93.1	*	*
BGDis-B [369]	2020	90.8	*	*
BGGDis-B [369]	2020	94.6	*	*
LDA [374]	2020	97.0	100	92.0
MOPSO [375]	2019	91.9	95.8	86.3
NSGA-II [375]	2019	90.4	93.1	85.2
MOEA/D [375]	2019	90.2	94.5	84.2

Average accuracies obtained from each category of the studied literature models, i.e. ANN-based, SVM-based, rule/fuzzy-based, tree-based, KNN-based and other ones, for WBCD classification are shown in **Fig 2.15**. As can be observed from this figure, the average accuracy of the investigated rule/fuzzy-based tools is higher than that of other categories.

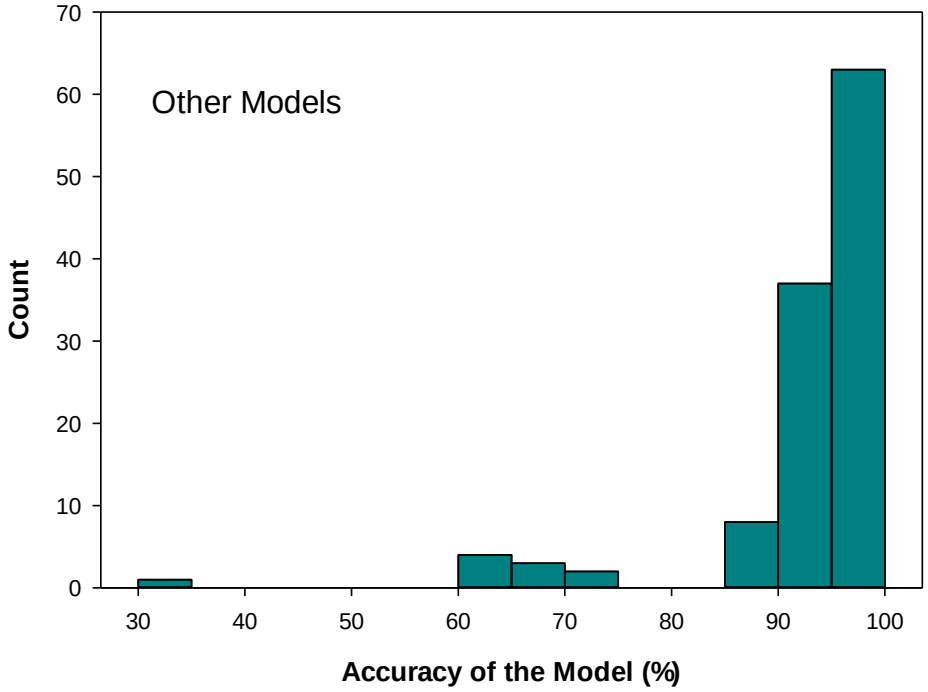


Fig. 2.14: Histogram of the accuracies obtained from other available models in the literature

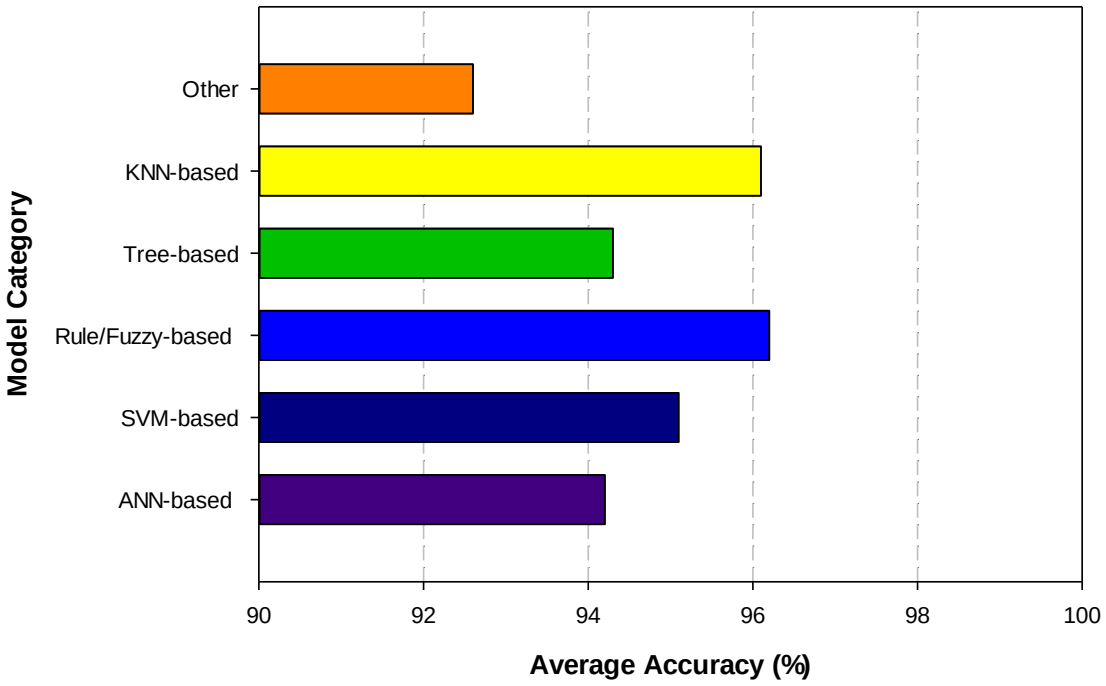


Fig. 2.15: Average accuracies obtained from the studied literature models for WBCD classification

2.6 SUMMARY AND CONCLUSION

A reliable diagnosis of BC is of great importance amongst the researchers, as it has a considerable impact on patients' lives. In addition to the laboratory tests and examinations for BC investigations, a group of researchers have focused on the application of artificial intelligence and MLDM approaches in the development of CAD systems for fast, reliable and inexpensive BC detection. As smart models are able to extract hidden knowledge from BC databases, these systems can pave the way for more advanced studies in this medical field.

Among all the available databases for BC, the WBCD is the most employed database for BC classification studies. This work identified papers on the application of MLDM approaches for WBCD classification, published between 1995 and 2020. The time scale of studies on the WBCD utilizing MLDM techniques indicates that the number of works has been increased over the years. The presented classification models in the reviewed papers were analysed according to some statistical parameters, including accuracy, sensitivity and specificity. As some papers just reported the accuracy of the proposed models, this parameter selected as the main variable for comparisons. This was the major limitation of our study.

Based on the obtained results, hybrid MLDM classifiers are generally effective in classifying the WBCD into malignant or benign cases. This shows the potential of the MLDM approaches for BC detection, especially at the early stages. Further implementation and improvements of the predictive modeling techniques for BC classification can pave the way for better medical diagnostic decision support systems.

Indeed, the majority of the reviewed hybrid MLDM algorithms like CWV-BANN-SVM model [304], RST-KNN [356], and GA-RotationF [301] have flexible capability of nonlinear modeling. Hence, it can be concluded that a combination of machine learning algorithms and optimization techniques can lead to higher accuracy and precision. However, as some approaches are known to

be black boxes, the resulting model might not be clear and could not be easily understood by non-experts like physicians.

2.7 RECOMMENDATIONS

The main recommendations for future studies are summarized as follows:

- This work just investigated the MLDM models for the WBCD. It is recommended to review the studies on the application of MLDM techniques in modeling other databases like MIAS, IRMA and DDSM.
- According to some studies, employing feature extraction techniques may boost the overall performance of the employed classifier. Hence, evaluating different feature extraction techniques should be considered.
- Hybrid models like provided excellent outcomes for the WBCD classification. It is recommended to assess the sustainability of different hybrid models on different datasets.
- In the case of small datasets like the WBCD, the speed of the employed MLDM technique might not be significant. However, slow performance caused by massive computations is a problem to be solved when big databases are employed. Therefore, researchers are encouraged to evaluate the models in terms of computation speed as well.
- Last but not least, having a thorough database with a sufficient number of features for BC can help to build more reliable and novel CAD systems. Hence, in addition to employing the available databases for BC, the development of an extensive database for BC investigations is also recommended.

Abbreviations

ACO	ant colony optimization
ACR	American College of Radiology
AIRS	artificial immune recognition system
AM	artificial metaplasticity
AM	artificial meta-plasticity
ANFCLH	adaptive neuro-fuzzy classifier with the linguistic hedges
ANFIS	adaptive neuro-fuzzy inference system
ANN	artificial neural network
ART	adaptive resonance theory
ART	association rule
ASCO	American Society of Clinical Oncology
ASI	assistant-I
ASR	age-standardized rates
ASR	assistant-R
B	Bayesian inference
BC	Breast cancer
BFS	Bayesian feature selection
BGD	batch gradient descent
BGDis	Bounded Gaussian distribution
BGDM	batch gradient descent with momentum
BGGDis	Bounded generalized Gaussian distribution
BI-RADS	Breast Imaging Reporting and Data System
BN	Bayes net
BP	back-propagation
BSO	brain storm optimization
CADe	computer aided detection
CADx	computer aided diagnosis
CART	Classification and regression tree
CBR	case-based reasoning
CC	cooperative coevolution

CFSSE	CFS subset evaluation
CG	conjugate gradient
CGCRMM	classification rules mining model with GA in cloud computing
CGNFC	conjugate gradient neuro-fuzzy classifier
CL	competitive learning
COSE	consistency subset evaluation
CS	Cuckoo search
CSA	crow search algorithm
CSAE	Chi squared attribute evaluation
CSE	classifier subset evaluation
CSO	cat swarm optimization
DBN	deep belief network
DDSM	Digital Database for Screening Mammography
DFNN	deep feed-forward neural network
DPCCM	discriminating partial correlation coefficient metric
DT	Decision tree
EA	evolutionary algorithm
EIS	evolutionary IS
EKF	extended Kalman filter
EVEN	evolutionary ensemble classifiers
FAE	filtered attribute evaluation
FAEMODE	Multi objective Differential Evolution for feature selection
FAIS	fuzzy-artificial immune system
FARTMAP	fuzzy ARTMAP
FCM	fuzzy C-means
FE	fuzzy entropy
FEBFC	fuzzy entropy-based fuzzy classifier
FEM	fuzzy entropy measure
FF	feed forward
FFDM	full-field digital mammography
FGPNN	fuzzy Gaussian potential neural network

FL	Fuzzy logic
FMM	fuzzy min-max
FRNN	fuzzy-rough nearest neighbor
FRPCA	Fuzzy robust principal component analysis
FSAM	fuzzy SAM
FSE	filtered subset evaluation
FSM	feature space mapping
FSRAIRS	fuzzy SVM-RWTS AIRS
GA	Genetic Algorithm
GA-MOO-ANN	GA-based Pareto-optima and ANN
GAOGB	genetic algorithm-based online gradient boosting
GCCD	Greenfield–Chiclana Collapsing Defuzzifier
GD	gradient descent
GDis	Gaussian distribution
GDX	gradient descent with adaptive momentum and step sizes
GGDis	Generalized Gaussian distribution
GNRBA	Gauss-Newton representation-based algorithm
GO	generally optimized
GP	genetic programming
GR	general regression
GRAE	gain ratio attribute evaluation
GTO	global tree optimization
HFNN	hierarchical fuzzy neural network
HMM	hybrid hidden Markov model
HRCNN	hyper-rectangular composite neural network
HSS	half selection strategy
IDRSA	improved dominance-based rough set
IG	information gain
IGAE	information gain attribute evaluation
IRMA	Image Retrieval in Medical Applications
IRSS	influential rule search scheme

IS	isotonic separation
KDE	kernel density estimation
KLR	kernel logistic regression
KM	Koza's model
KMIP	Karnik–Mendel iterative procedure
KNN	K-nearest neighbour
KNNE	KNN ensemble
KPCA	kernel principal component analysis
KRNN	k-rank nearest neighbour
LDA	linear discriminant analysis
LFC	look ahead feature construction
LHNFCSF	linguistic hedges neuro-fuzzy classifier with selected features
LLR	Laplace and logistic regression
LLW-ANN	local linear wavelet ANN
LM	Levenberg-Marquardt
LN	logical network
LR	logistic regression
LS-SVM	least squares version of SVM
LSA	logarithmic simulated annealing
LVQ	learning vector quantization
MBL	memory based learner
MF	membership function
MI	mutual information
MIAS	Mammographic Image Analysis Society
ML	Maximum likelihood
MLDM	machine learning and data mining
MLP	multi-layer perceptron
MOE	mixture of experts
MOEA/D	multi objective evolutionary algorithm based on decomposition
MOPSO	multi-objective particle swarm optimization
MP	memetic pareto

MRI	magnetic resonance imaging
MSS	mean selection strategy
MTO	mother tree optimization
MTOCL	MTO algorithm with climate change
NB	Naïve Bayesian
NFE	NF ensemble
NNTS	neural network for threshold selection
NSGA-II	non-dominated sorting genetic algorithm
OWA	ordered weighted averaging
P-ANN	probabilistic ANN
PCA	principal component analysis
PET	Positron Emission Tomography
PNCF	parallel neural-based clusters fusion
PNSCF	parallel neural-based strong clusters fusion
PPA	Parasitism-Predation algorithm
PSO	Particle Swarm Optimization
QC	quadratic classifier
QCE	QC ensemble
QDA	quadratic discriminant analysis
QN	Quasi-Newton
R-ANN	recurrent ANN
RAE	relief attribute evaluation
RBF	radial basis function
RF	rotation forest
RIAC	rule induction algorithm based on the approximate classification
RIW	randomly initialized weight
RLS	recursive least square
RST	rough set theory
RT	random tree
SBS	sequential backward selection
SCANN	combining classifiers by using correspondence analysis

SCG	scaled conjugated gradient
SFFS	sequential floating forward selection
SFS	sequential forward selection
SMOTE	synthetic minority over-sampling technique
SNB	semi-Naïve Bayesian
SOM	self-organizing map
SSCGNFC	scaled conjugate gradient neuro-fuzzy classifier
SSV	separability split value
SUASE	symmetric uncertainty attribute set evaluation
SVM	support vector machine
SVMAE	SVM attribute evaluation
T2FLS	type-2 fuzzy logic system
TGC	traditional genetic classification
TrEnL	transformed ensemble learning
VPMCD	variable predictive model-based class discrimination
W-ANN	wavelet ANN
W-NB	weighted NB
WBCD	Wisconsin Breast Cancer Database
WDBC	Wisconsin Diagnostic Breast Cancer Database
WMV	weighted majority vote
WOA	whale optimization algorithm

Acronyms

fn	false negative
fp	false positive
tn	true negative
tp	true positive

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3 APPLICATION OF DECISION TREE-BASED ENSEMBLE LEARNING IN THE CLASSIFICATION OF BREAST CANCER

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PREFACE

This manuscript is submitted to … for possible publication.

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Contribution: writing the original draft**;** classification modeling; error analysis; revision of the original draft based on the comments of co-author

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ABSTRACT

As a common screening and diagnostic tool, Fine Needle Aspiration Biopsy (FNAB) of the suspicious breast lumps can be used to distinguish between malignant and benign breast cytology. In this study, we first review published works on the classification of breast cancer where the machine learning and data mining algorithms have been applied by using the Wisconsin Breast Cancer Database (WBCD). This work then introduces effective new tools, based on Random Forest (RF) and Extremely Randomized Trees or Extra Trees (ET) algorithms, for classification of the breast cancer. The RF and ET strategies use the decision trees as proper classifiers to attain the ultimate classification. The RF and ET approaches include four main stages; namely input identification, determination of optimal number of trees, voting analysis, and final decision. The models implemented in this research consider important factors such as uniformity of cell size, bland chromatin, mitoses, and clump thickness as the input parameters. According to the statistical analysis, the proposed methods are able to accurately classify the type of breast cancer. The error analysis results reveal that the designed RF and ET models offer the most reliable outcomes and the highest diagnostic performance, compared to previous tools/models in the literature for the WBCD classification. The highest and lowest relative importance are attributed to uniformity of cell size and mitoses among the factors. It is expected that RF and ET algorithms play an important role in medicine and health systems for the purposes of screening and diagnosis in the near future.

KEYWORDS: Breast Cancer; Wisconsin Breast Cancer Database; Classification; Ensemble Learning; Random Forest/Extra Trees

3.1 INTRODUCTION

3.1.1 Breast cancer overview

It is believed that the most common recognized type of cancer among women is breast cancer. Although breast cancer can occur in men, it is very rare. According to the research work [1], one out of every eight U.S. women might be affected by breast cancer during her lifetime. Another report claims that the breast cancer comprises 25% of all predicted cancer cases in Canadian women in 2017 [2].

Different sections of the breast such as ducts and glands might be the start point of breast cancers. If the cancer cells are able to enter the lymph system or bloodstream, the breast cancer will spread to other parts of the body [3]. Adenomas, fibromas (fibroids), a soft fibroma of the eyelid, hemangiomas, and lipomas are examples of the benign tumors [4]. It is worth noting that benign breast lumps (or non-cancerous breast tumors) are not in the category of cancers. Indeed, development of malignant tumors including carcinoma, sarcoma, and blastoma in the breast tissues is responsible for breast cancer occurrence. In addition to the benign and malignant tumors, some tumors such as actinic keratosis, dysplasia of the cervix, and leukoplakia can be classified as premalignant tumors [4].

Although considerable improvements on breast cancer investigations have been made in recent years, the main causes of breast cancer still remain obscured in the majority of cases [5]. Factors such as increasing age, obesity, a family history, estrogen exposure, alcohol consumption, and inheritance of susceptibility genes are normally associated with the development of breast cancer [5-11]. The above factors represent the indicators of risk that can be helpful when differentiating between women with different levels of risk. Therefore, the parameters are called “risk factors” [12].

Early diagnosis of breast cancer using appropriate approaches may lead to a decrease in mortality rates of women [13, 14]. Although malignancy or benignity of the breast mass can be detected through surgical biopsy, this method is a costly and time-consuming operation. Moreover, the surgical biopsy has a negative influence on the psychology of the patient [15, 16]. For proper treatment of patients suffering from breast cancer, resident experts need to work as a team on the important corresponding aspects such as oncology, radiology, and surgery. Surgical treatment, systemic therapy, radiation therapy, and minimally invasive therapies might be applied, depending on the patient health conditions and type of cancer. More information can be found elsewhere [5].

At-risk women (starting at age 40) can be screened for breast cancer using mammography, which is the most employed approach in clinics and hospitals [5]. However, this method is not always

accessible in poor, and underdeveloped/developing countries [17]. To screen the high-risk patients, in addition to mammography, the magnetic resonance imaging (MRI) method can be implemented [18]. A common technique, which is also used as a diagnostic and screening approach for investigation and diagnosis of the breast cancer, is Fine Needle Aspiration Biopsy (FNAB) [17, 19, 20]. FNAB is a quick and simple procedure that is relatively less traumatic, compared to the surgical biopsy. Specimens of FNA are commonly obtained through utilizing 20- to 25-gauge needles [21].

The Wisconsin Breast Cancer Database (WBCD) reports breast cancer-related measurements, according to the FNAB data. A FNAB is prepared through aspiration of a small drop of a viscous fluid from the breast mass using a needle [22]. Each dataset contains nine cytological characteristics of malignant or benign breast fine needle aspirates. Indeed, this database provides comprehensive data that can be employed for the distinction between the benign and malignant breast masses.

3.1.2 Study objectives

In the past few years, researchers developed several predictive models capable of classifying breast cancer types. For example, in 2018, Fondón et al. [23] employed Support Vector Machine (SVM) for breast cancer classification. In another study, Naive Bayes classification was used to classify the breast cancer data as malignant or benign [24]. Recently, Zhu et al. [25] investigated the performance of deep learning for distinguishing between molecular subtypes of breast cancer. The main goal of this study is to evaluate the performance of two ensemble methods, namely Random Forest (RF) and Extra Trees (ET), in the classification of WBCD. To the best of the authors' knowledge, this is the first work that presents simple visualized models based on the ET methodology in conjunction with the Classification and Regression Tree (CART) method to classify the WBCD.

To achieve the study goal, the remainder of the current work is organized into four sections. The related works on the WBCD classification using the machine learning and data mining approaches are reviewed in Section 3.2. Next, the RF and ET classification theory as well as the model

development procedure are briefly explained in Section 3.3. Using the WBCD and applying RF/ET methods, the research results and systematic discussion are then presented in Sections 3.4 and 3.5. The last section, Section 3.6, concludes the research investigation.

3.2 PREVIOUS WORKS

There are several studies in the open source literature that focus on classification of breast cancer which rely on the WBCD database through employing various mathematical methods, statistical models/algorithms, machine learning, and data mining approaches. In the context of development of intelligent/smart classification models for breast cancer classification, the main implemented approaches are Artificial Neural Networks (ANNs) [26-33], Fuzzy Logic (FL) [34-38], and SVMs [39-44]. Other methods, including linear programming [45], Learning Vector Quantization (LVQ) [46], decision trees [47] and K-nearest neighbor [48], are also investigated in the literature.

Application of feed-forward ANN with Back-Propagation (BP) in breast cancer classification was evaluated by Paulin, Santhakumaran [49]. They used different variations of the BP including batch training, Batch Gradient Descent (BGD), batch gradient descent with momentum, conjugate gradient, Quasi-Newton (QN), Levenberg-Marquardt (LM), and resilient BP to adjust the weights. The only criterion used in the work to evaluate the classification performance of the models was accuracy. Other parameters such as relative precision and recall were not calculated for the BP-based models. Among the studied training algorithms, the LM provided the best results [38].

In 2016, Abdel-Zaher, Eldeib [50] suggested a breast cancer classifier through employing a two-phase framework. The first phase includes an ANN in conjunction with the conjugate gradient back-propagation algorithm or LM. This pre-training phase is then followed by an unsupervised phase. This method is known as a Deep Belief Network Neural Network (DBN-NN). In addition to the DBN-NN, the researchers provided two other models based on the Randomly Initialized Weight BP Neural Network (RIW-BPNN). Their results revealed that the DBN-NN approach presents a greater

accuracy than the RIW-BPNN method. Although the DBN-NN method is capable of classifying the WBCD with satisfactory accuracy, it requires considerable effort to build a classification model using commercial technology [39]. This is considered as the main limitation for this technique.

Recently, Pota, Esposito, De Pietro [51] developed several rule-based fuzzy systems. Their work presented a procedure based on applying the naïve Bayes hypothesis to fuzzy systems. The employed optimization algorithms to find the fuzzy sets position, rule weights, and rule consequents are likelihood fuzzy analysis and neural networks. Although FL systems generally provide accurate results, the designing process is thorny and needs several implementation stages [40].

Ibrikci, Ustun, Kaya [52] investigated the WBCD by utilizing two classification models. These approaches are presented based on the conventional SVM and the combined kernel SVM (k-SVM) algorithms. Comparing the two developed models revealed that the k-SVM algorithm outperforms the standard version of SVM in terms of accuracy and reliability. In another study [53], the least squares version of SVM (LS-SVM) was used for classifying the WBCD. The main advantage of the SVM-based classification model over most of the FLs and neural networks is its simplicity and process speed [42].

Although the classification strategies employed in the literature offer reliable outcomes in the realm of breast cancer studies, this important health matter needs more precise and user-friendly tools. In a published study [54], the RF method is used as the weak learner. Then, ensembles of bagging, AdaBoost, dagging, multi boost, random subspace, and decorate were employed to develop a breast cancer classification model. However, in this study, RF is utilized as an ensemble model and the weak learner is the classification and regression tree (CART) model. In another study [55], the researchers developed two RF-based models employing 10 and 100 decision trees as weak learners. However, there is no information available regarding the structure of the created RF models. Furthermore, the accuracy of their predictive model is not satisfactory. Tripoliti et al. [56] proposed a model for the classification of WBCD which is based on RF with multiple estimators. 42 decision

trees were used in the best obtained forest. Ahmad and Yusoff [57] also implemented RF classifier for WBCD classification. A recent published study by Murugan et al. discusses about the application of RF in classification of WBCD [58]. In 2019, Hosni et al. [59] reviewed the published works on the application of different ensemble methods in the breast cancer research area. According to their study, the WBCD is the most frequently used database by researchers to perform experiments and modeling related to the breast cancer.

3.3 CLASSIFICATION PROCEDURE

3.3.1 WBCD

The WBCD was used to develop RF and ET classification models capable of classifying breast cancer into the benign or malignant case. The WBCD was originally presented by Dr. William H. Wolberg at the University of Wisconsin Hospitals in Madison [45]. **Table 3.1** gives further information regarding the dataset employed for the RF and ET modeling.

Table 3.1: Information about the refined WBCD.

Feature	Range	Average
Uniformity of Cell Size	1-10	4.442
Uniformity of Cell Shape	1-10	3.151
Bare Nuclei	1-10	3.215
Single Epithelial Cell Size	1-10	2.830
Bland Chromatin	1-10	3.234
Normal Nucleoli	1-10	3.545
Clump Thickness	1-10	3.445
Marginal Adhesion	1-10	2.870
Mitoses	1-10	1.603

This database contains 699 records where 241 (34.5%) are categorized as “malignant” and 458 (65.5%) are classified as “benign”. Excluding the ID number, the WBCD has nine independent attributes. Each characteristic is graded with a value ranging from 1 to 10; 1 denotes a typical benign and 10 represents a typical malignant. There are some patters in the databank of WBC with missing values (16 data series). These incomplete datasets are removed from the databank before the modeling process in this research work. The remaining data points contain 239 malignant and 444 benign cases.

3.3.2 Methodology

Ensembles are the methods that utilize several weak learners and aggregate the outcomes of them to develop a robust model. In this section, two ensemble methodologies, namely RF and ET, are briefly described.

RF method. Originally, the RF model was developed by Breiman and Cutler [60]. As an ensemble methodology, RF employs a number of decision trees as weak classifiers or regressors. During the learning phase, randomness can be introduced to attain certain relationships between the trees grown on the same training set. Each node of the tree has access to only one randomly chosen subset of features, while training a decision tree in the RF approach.

Commonly, the RF employs the CART algorithm, introduced by Breiman, Friedman, Stone, Olshen [61], as a weak classifier to develop a strategy for classification tasks. In the CART method, the input space is separated into several rectangular or cuboid regions that are non-overlapping [62-64]. To train each CART, different sub-datasets of the training points are chosen with replacement. After construction of CARTs through using bootstrap samples, the remaining data, i.e. the data which are not utilized in the CART construction, are used to determine the model’s error and feature importance. For each CART, about 35% of the data series are left out of the bootstrap samples. These data are called Out-Of-Bag (OOB) cases.

Using RF, a random instance of p' features is drawn at each CART split. The original work suggests that $p' = \sqrt{p}$, where *p* is the total number of features. Considering a training set including *D* with *n* samples, the RF algorithm is as follows:

RF General Algorithm

1: generate *m* bootstrap samples $D_1, D_2, \ldots, D_m$
2: **for** each *i* in [1, *m*] **do**
3: grow a tree predictor $\hat{f}_i^*$ using the CART method, that:
4: at each split $p' \langle p$ random variables are selected.
each CART is fully grown and not pruned.
5: **end for**
6: classification of a parameter like *x* using ensemble of the CARTs:
the most voted class

With the aim of computing the importance of each feature of the investigated database, Gini measurements or permutations can be used in the RF method. This study applies the Gini importance. Consider that there is a total number of *n* samples at node τ. Through defining $p_k = n_k / n$ as the n_k samples' fraction from $k = \{0,1\}$ category out of all the samples at node τ, the following expression calculates the Gini impurity [65]:

$$i(\tau) = 1 - {p_1}^2 - {p_0}^2 \qquad (3.1)$$

where $i(\tau)$ stands for the Gini impurity. Consequently, Equation (2) defines the decrease of $i(\tau)$ that follows from splitting and sending the instances to sub-nodes τ_1 and τ_2 by a threshold t_θ on feature θ as follows [65]:

$$\Delta i(\tau) = i(\tau) - p_l i(\tau_1) - p_r i(\tau_2) \qquad (3.2)$$

where $p_l = n_l / n$ and $p_k = n_k / n$ introduce the sample fractions.

Over all features existing at the node, a thorough search is performed. Conducting this stage, the pair $\{\theta, t_\theta\}$ responsible for a maximal Δi is obtained. Then, a decrease in $i(\tau)$ as a result of the optimal split $\Delta i_\theta(\tau, T)$ is recorded and accumulated for all nodes in all CARTs, individually for all features; *T* refers to the tree. Finally, the Gini importance, $I_G(\theta)$, is determined by the following expression:

$$I_G(\theta) = \sum_T \sum_\tau \Delta i_\theta(\tau, T) \qquad (3.3)$$

ET method. As an ensemble of randomized trees, the ET technique increases the randomization of the RF algorithm [66]. Similar to RF, the ET technique is computationally effective and is capable of dealing with high dimensional input vectors. However, considering the training time, ET overcomes the RF method. This is owing to a simpler procedure of ET to choose the thresholds. Furthermore, as compared to the RF, increased randomization of the ET reduces the variance [66]. Unlike RF, each tree in the ET is trained using the total training data points (in an autonomous way). Within the phase of ET learning, CARTs are created (in a supervised manner) from the introduced databank of *p*-dimensional samples and the corresponding targets.

The following expression represents the score measure in ET classification [66]:

$$Score_C(s, S) = \frac{2 I_C{}^S(S)}{H_S(S) + H_C(S)} \qquad (3.4)$$

in which, S and s are the sample and split, respectively; the split entropy and classification entropy are indicated by $H_S(S)$ and $H_C(S)$, respectively; and $I_C{}^S(S)$ indicates the mutual information of the classification and the split outcome. In regression, the relative variance reduction can be employed [66].

As mentioned earlier, unlike RF, the randomness of ET comes from the random splits of all data points. Indeed, in the ET method, nodes are split using random subsets of features. The following pseudo-code shows the procedure to pick a random split in the ET [66].

Pseudo-code to pick a random split (*S*,*a*)

1: *Input*: an attribute *a* and a training set *S*
2: *Output*: a split
3: Categorical attribute *a* (denoted by *A*)
4: Compute the subset of *A* of values of *a* that available in S (A_S);
5: Randomly draw an appropriate non-empty subset A_1 of A_S and a subset A_2 of A/A_S; and
6: Return the split [$a \in A_1 \cup A_2$].

2.3.3 Model Development

Prior to utilizing the refined WBCD to implement the RF and ET methodologies, the collected data points are randomly divided into two sub-groups including training and testing sub-datasets. Commonly, 75-90% of the entire database are used in the training phase while employing connectionist predictive tools. In this study, 85% of the entire dataset are allocated for the training state. The remaining data points, 15%, are utilized to evaluate the capability of the developed RF and ET models in classifying the unseen data. Simple schematic of the procedure for RF/ET model development to classify the WBCD is presented in **Fig. 3.1**.

It should be mentioned that instead of allocating a part of total data points for a validation phase, 10-fold cross validation procedure is employed for training the models. Using the cross-validation method results in having more samples, as training data points, to develop a more reliable model. This study leads to development of the RF/ET classification models with the best obtainable results for categorization of the WBCD. As the next stage, after data pre-processing, the number of CARTs

in the RF and ET methodologies is altered from two to ten. The input parameters to develop the models are explained below.

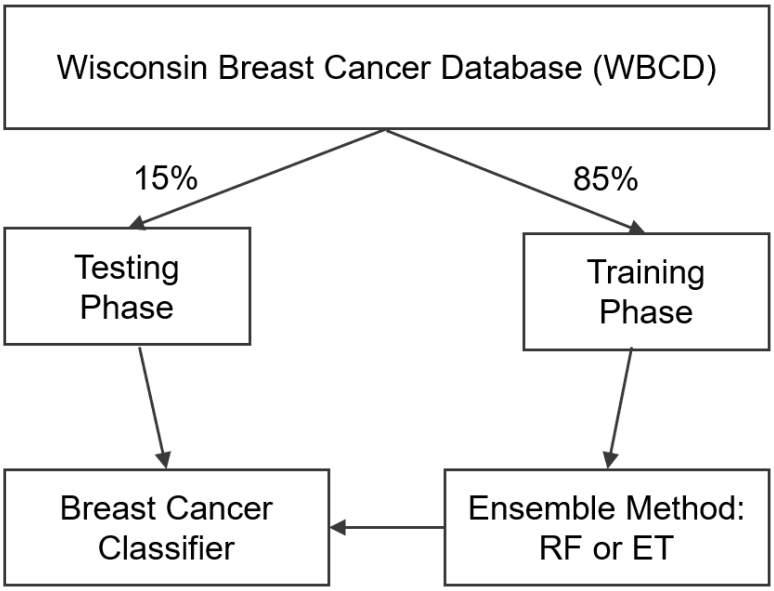


Fig. 3.1: A simple procedure for RF/ET model development to classify the WBCD

The cells grouping in the breast are described with the clump thickness. While malignant cells are generally categorized in multiple layers, benign cells are often grouped in monolayers. Despite the benign cells, the malignant cells are equally distributed. In the WBCD, the variations in shape and size of the cells are described by the uniformity of shape/size. The parameter namely "single epithelial cell size" is strongly connected to the previous parameters. Epithelial cells with considerable enlargement might be an indication of malignancy. Unlike the malignant cells, there is a tendency for benign cells to stick together. To illustrate this property, the marginal adhesion is used. Nuclei lacking cytoplasm is demonstrated by bare nuclei. Cells that exhibit this phenomenon are most likely malignant. The nucleus texture is taken into account using the bland chromatin. Indeed, coarse texture is a sign of malignancy. On the other hand, the texture uniformity is a sign of benign. WBCD uses the normal nucleoli to describe the small structures existing in the nucleus. The

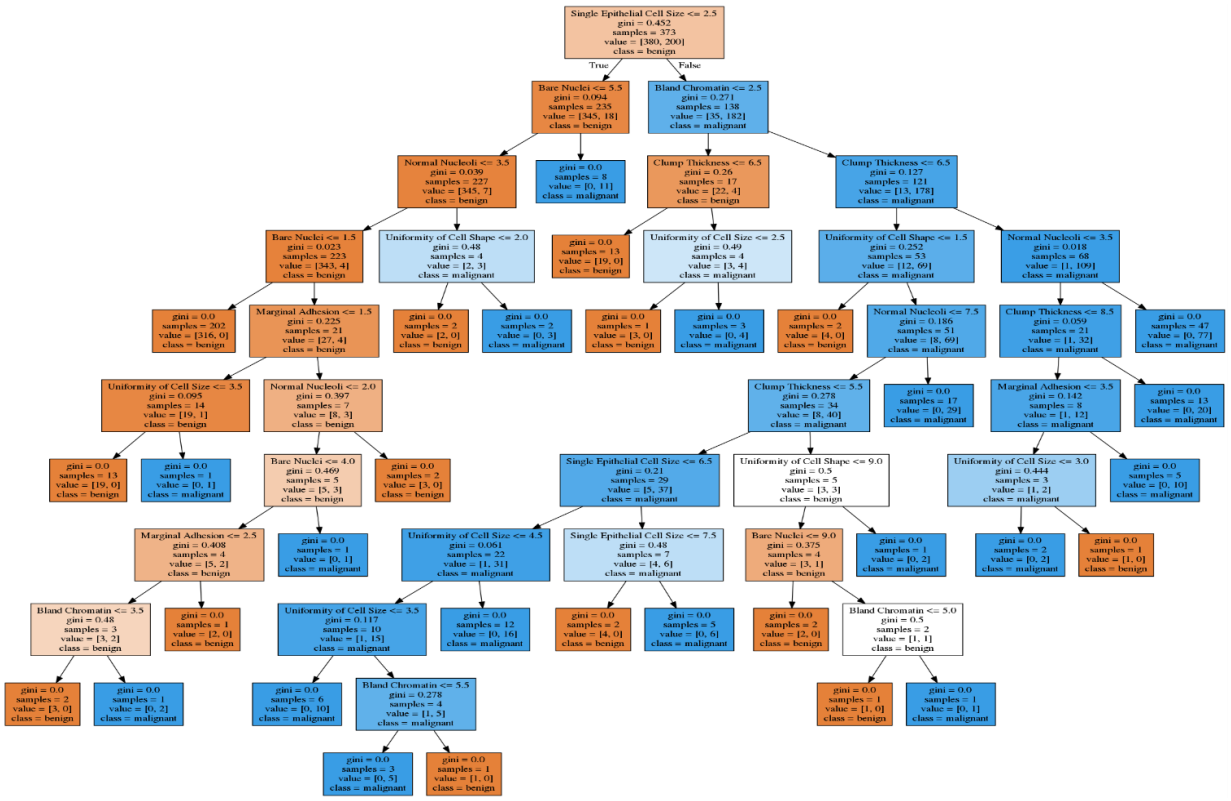
nucleoli, which is normally very small, starts to be prominent in the malignant cells. The cell division is defined as mitosis. The number of mitotic divisions can help cancer specialists to determine the malignancy [40-43, 50].

It should be noted that the test trials for effective construction of a RF/ET model for classification of the breast cancer into two sub-classes are performed on PyCharm Community Edition 3.1.3 using a PC with an Intel® Core™ i7-Q740 @ 1.73-2.93 GHz CPU and 8.00 GB RAM.

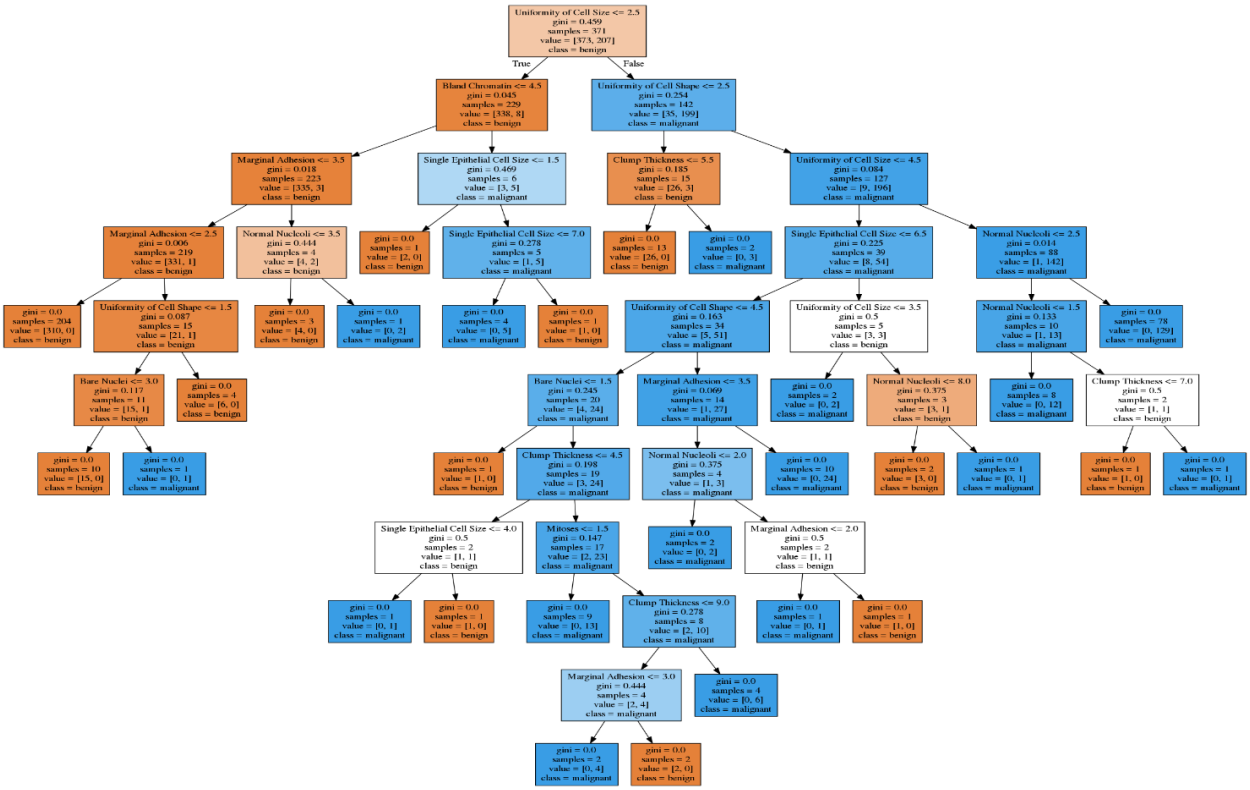
3.4 RESULTS

To assess the performance of the developed RF/EF classification models for WBCD, the magnitudes of three important statistical parameters including Classification Accuracy (ACC), precision or Positive Predicted Value (PPV), and recall or True Positive Rate (TPR) are obtained.

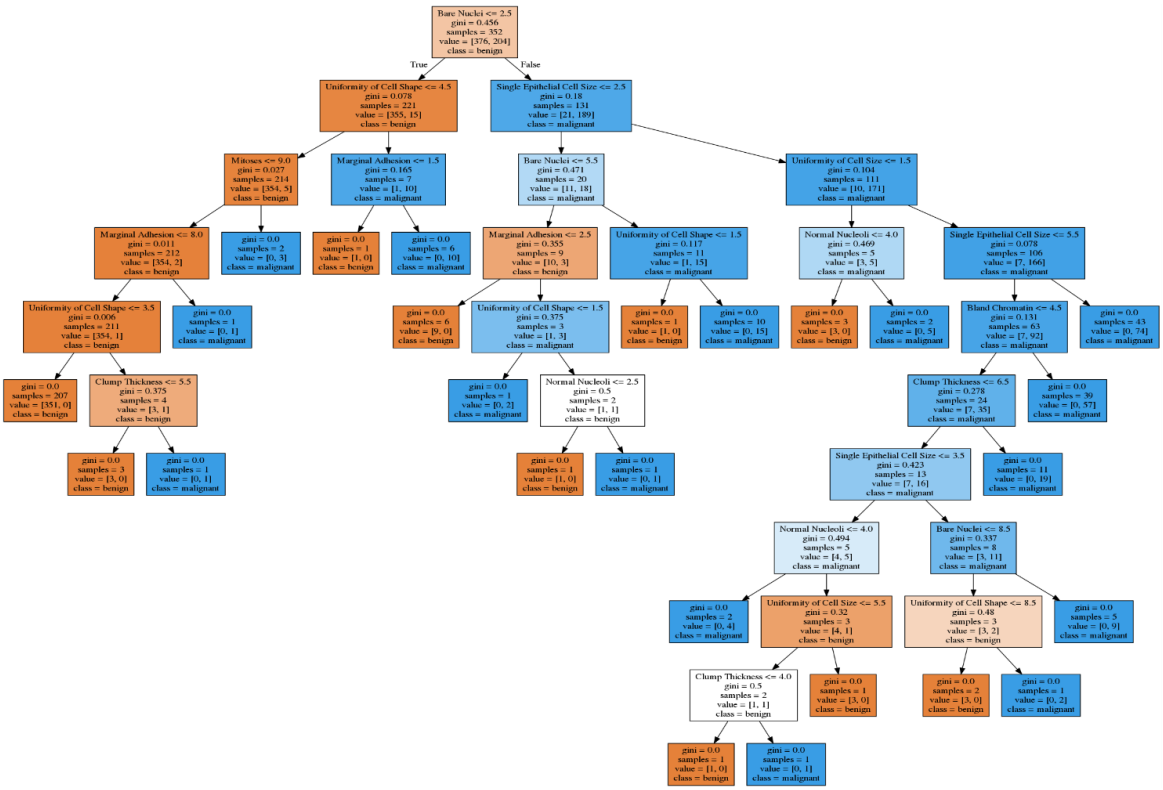
Based on the error analysis results, it was found that all the developed RF and ET models, except for the RF model with three CARTs and the ET model with two CARTs, are able to precisely (and reliably) classify the breast cancer type for all the data utilized in this research work. In other words, the obtained values of ACC, PPV, and TPR for the developed RF and ET models with three (just for the ET model), four, five, six, seven, eight, nine, and ten CARTs in the model structure are equal to 1.0000, implying a significant performance of the RF and ET methods. **Figs. 3.2** and **3.3** show the constructed CARTs during the development of the RF model with four CARTs and the ET model with three CARTs, respectively.


Single Epithelial Cell Size <= 2.5
gini = 0.452
samples = 373
value = [380, 200]
class = benign
True
False
Bare Nuclei <= 5.5
gini = 0.094
samples = 235
value = [345, 18]
class = benign
Bland Chromatin <= 2.5
gini = 0.271
samples = 138
value = [35, 182]
class = malignant
Normal Nucleoli <= 3.5
gini = 0.039
samples = 227
value = [345, 7]
class = benign
gini = 0.0
samples = 8
value = [0, 11]
class = malignant
Clump Thickness <= 6.5
gini = 0.26
samples = 17
value = [22, 4]
class = benign
Clump Thickness <= 6.5
gini = 0.127
samples = 121
value = [13, 178]
class = malignant
Bare Nuclei <= 1.5
gini = 0.023
samples = 223
value = [343, 4]
class = benign
Uniformity of Cell Shape <= 2.0
gini = 0.48
samples = 4
value = [2, 3]
class = malignant
gini = 0.0
samples = 13
value = [19, 0]
class = benign
Uniformity of Cell Size <= 2.5
gini = 0.49
samples = 4
value = [3, 4]
class = malignant
Uniformity of Cell Shape <= 1.5
gini = 0.252
samples = 53
value = [12, 69]
class = malignant
Normal Nucleoli <= 3.5
gini = 0.018
samples = 68
value = [1, 109]
class = malignant
gini = 0.0
samples = 202
value = [316, 0]
class = benign
Marginal Adhesion <= 1.5
gini = 0.225
samples = 21
value = [27, 4]
class = benign
gini = 0.0
samples = 2
value = [2, 0]
class = benign
gini = 0.0
samples = 2
value = [0, 3]
class = malignant
gini = 0.0
samples = 1
value = [3, 0]
class = benign
gini = 0.0
samples = 3
value = [0, 4]
class = malignant
gini = 0.0
samples = 2
value = [4, 0]
class = benign
Normal Nucleoli <= 7.5
gini = 0.186
samples = 51
value = [8, 69]
class = malignant
Clump Thickness <= 8.5
gini = 0.059
samples = 21
value = [1, 32]
class = malignant
gini = 0.0
samples = 47
value = [0, 77]
class = malignant
Uniformity of Cell Size <= 3.5
gini = 0.095
samples = 14
value = [19, 1]
class = benign
Normal Nucleoli <= 2.0
gini = 0.397
samples = 7
value = [8, 3]
class = benign
Clump Thickness <= 5.5
gini = 0.278
samples = 34
value = [8, 40]
class = malignant
gini = 0.0
samples = 17
value = [0, 29]
class = malignant
Marginal Adhesion <= 3.5
gini = 0.142
samples = 8
value = [1, 12]
class = malignant
gini = 0.0
samples = 13
value = [0, 20]
class = malignant
gini = 0.0
samples = 13
value = [19, 0]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
Bare Nuclei <= 4.0
gini = 0.469
samples = 5
value = [5, 3]
class = benign
gini = 0.0
samples = 2
value = [3, 0]
class = benign
Single Epithelial Cell Size <= 6.5
gini = 0.21
samples = 29
value = [5, 37]
class = malignant
Uniformity of Cell Shape <= 9.0
gini = 0.5
samples = 5
value = [3, 3]
class = benign
Uniformity of Cell Size <= 3.0
gini = 0.444
samples = 3
value = [1, 2]
class = malignant
gini = 0.0
samples = 5
value = [0, 10]
class = malignant
Marginal Adhesion <= 2.5
gini = 0.408
samples = 4
value = [5, 2]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
Uniformity of Cell Size <= 4.5
gini = 0.061
samples = 22
value = [1, 31]
class = malignant
Single Epithelial Cell Size <= 7.5
gini = 0.48
samples = 7
value = [4, 6]
class = malignant
Bare Nuclei <= 9.0
gini = 0.375
samples = 4
value = [3, 1]
class = benign
gini = 0.0
samples = 1
value = [0, 2]
class = malignant
gini = 0.0
samples = 2
value = [2, 0]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
Bland Chromatin <= 3.5
gini = 0.48
samples = 3
value = [3, 2]
class = benign
gini = 0.0
samples = 1
value = [2, 0]
class = benign
Uniformity of Cell Size <= 3.5
gini = 0.117
samples = 10
value = [1, 15]
class = malignant
gini = 0.0
samples = 12
value = [0, 16]
class = malignant
gini = 0.0
samples = 2
value = [4, 0]
class = benign
gini = 0.0
samples = 5
value = [0, 6]
class = malignant
gini = 0.0
samples = 2
value = [2, 0]
class = benign
Bland Chromatin <= 5.0
gini = 0.5
samples = 2
value = [1, 1]
class = benign
gini = 0.0
samples = 2
value = [3, 0]
class = benign
gini = 0.0
samples = 6
value = [0, 2]
class = malignant
gini = 0.0
samples = 6
value = [0, 10]
class = malignant
Bland Chromatin <= 5.5
gini = 0.278
samples = 4
value = [1, 5]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
gini = 0.0
samples = 3
value = [0, 5]
class = malignant
gini = 0.0
samples = 1
value = [0, 1]
class = malignant

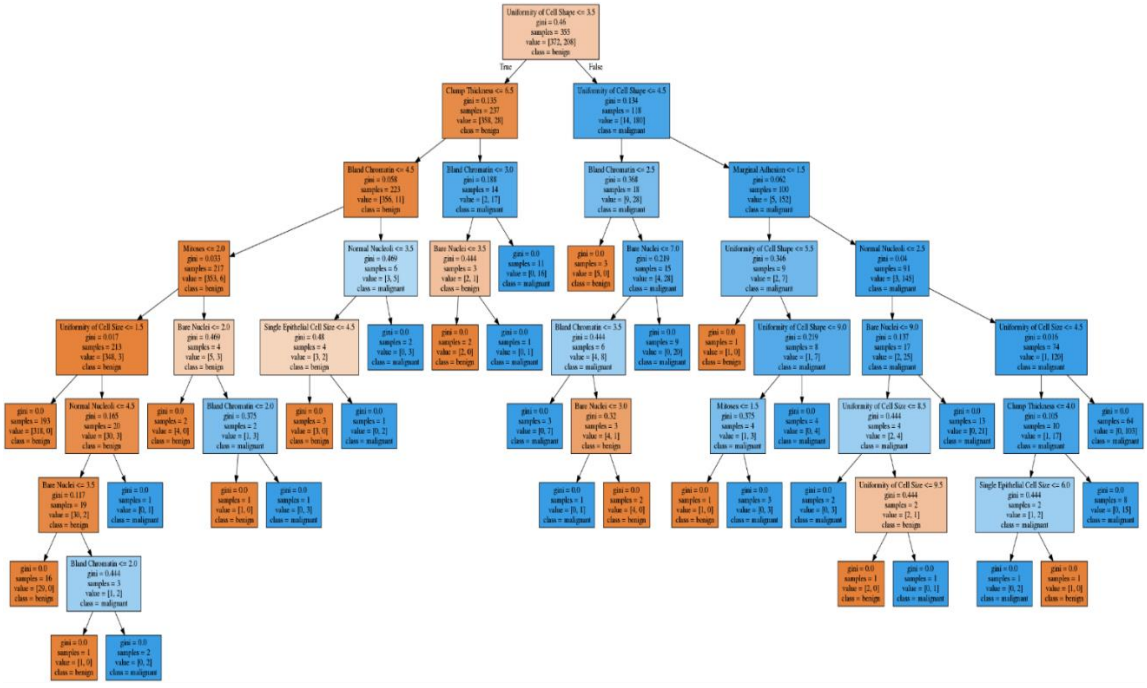
(a)


Uniformity of Cell Size <= 2.5
gini = 0.459
samples = 371
value = [373, 207]
class = benign
True
False
Bland Chromatin <= 4.5
gini = 0.045
samples = 229
value = [338, 8]
class = benign
Uniformity of Cell Shape <= 2.5
gini = 0.254
samples = 142
value = [35, 199]
class = malignant
Marginal Adhesion <= 3.5
gini = 0.018
samples = 223
value = [335, 3]
class = benign
Single Epithelial Cell Size <= 1.5
gini = 0.469
samples = 6
value = [3, 5]
class = malignant
Clump Thickness <= 5.5
gini = 0.185
samples = 15
value = [26, 3]
class = benign
Uniformity of Cell Size <= 4.5
gini = 0.084
samples = 127
value = [9, 196]
class = malignant
Marginal Adhesion <= 2.5
gini = 0.006
samples = 219
value = [331, 1]
class = benign
Normal Nucleoli <= 3.5
gini = 0.444
samples = 4
value = [4, 2]
class = benign
gini = 0.0
samples = 1
value = [2, 0]
class = benign
Single Epithelial Cell Size <= 7.0
gini = 0.278
samples = 5
value = [1, 5]
class = malignant
gini = 0.0
samples = 13
value = [26, 0]
class = benign
gini = 0.0
samples = 2
value = [0, 3]
class = malignant
Single Epithelial Cell Size <= 6.5
gini = 0.225
samples = 30
value = [8, 54]
class = malignant
Normal Nucleoli <= 2.5
gini = 0.014
samples = 88
value = [1, 142]
class = malignant
gini = 0.0
samples = 204
value = [310, 0]
class = benign
Uniformity of Cell Shape <= 1.5
gini = 0.087
samples = 15
value = [21, 1]
class = benign
gini = 0.0
samples = 3
value = [4, 0]
class = benign
gini = 0.0
samples = 1
value = [0, 2]
class = malignant
gini = 0.0
samples = 4
value = [0, 5]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
Uniformity of Cell Shape <= 4.5
gini = 0.163
samples = 34
value = [5, 51]
class = malignant
Uniformity of Cell Size <= 3.5
gini = 0.5
samples = 5
value = [3, 3]
class = benign
Normal Nucleoli <= 1.5
gini = 0.133
samples = 10
value = [1, 13]
class = malignant
gini = 0.0
samples = 78
value = [0, 129]
class = malignant
Bare Nuclei <= 3.0
gini = 0.117
samples = 11
value = [15, 1]
class = benign
gini = 0.0
samples = 4
value = [6, 0]
class = benign
Bare Nuclei <= 1.5
gini = 0.245
samples = 20
value = [4, 24]
class = malignant
Marginal Adhesion <= 3.5
gini = 0.069
samples = 14
value = [1, 27]
class = malignant
gini = 0.0
samples = 2
value = [0, 2]
class = malignant
Normal Nucleoli <= 8.0
gini = 0.375
samples = 3
value = [3, 1]
class = benign
gini = 0.0
samples = 8
value = [0, 12]
class = malignant
Clump Thickness <= 7.0
gini = 0.5
samples = 2
value = [1, 1]
class = benign
gini = 0.0
samples = 10
value = [15, 0]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
Clump Thickness <= 4.5
gini = 0.198
samples = 19
value = [3, 24]
class = malignant
Normal Nucleoli <= 2.0
gini = 0.375
samples = 4
value = [1, 3]
class = malignant
gini = 0.0
samples = 10
value = [0, 24]
class = malignant
gini = 0.0
samples = 2
value = [3, 0]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
Single Epithelial Cell Size <= 4.0
gini = 0.5
samples = 2
value = [1, 1]
class = benign
Mitoses <= 1.5
gini = 0.147
samples = 17
value = [2, 23]
class = malignant
gini = 0.0
samples = 2
value = [0, 2]
class = malignant
Marginal Adhesion <= 2.0
gini = 0.5
samples = 2
value = [1, 1]
class = benign
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
gini = 0.0
samples = 9
value = [0, 13]
class = malignant
Clump Thickness <= 9.0
gini = 0.278
samples = 8
value = [2, 10]
class = malignant
gini = 0.0
samples = 1
value = [0, 1]
class = malignant
gini = 0.0
samples = 1
value = [1, 0]
class = benign
Marginal Adhesion <= 3.0
gini = 0.444
samples = 4
value = [2, 4]
class = malignant
gini = 0.0
samples = 4
value = [0, 6]
class = malignant
gini = 0.0
samples = 2
value = [0, 4]
class = malignant
gini = 0.0
samples = 2
value = [2, 0]
class = benign

(b)

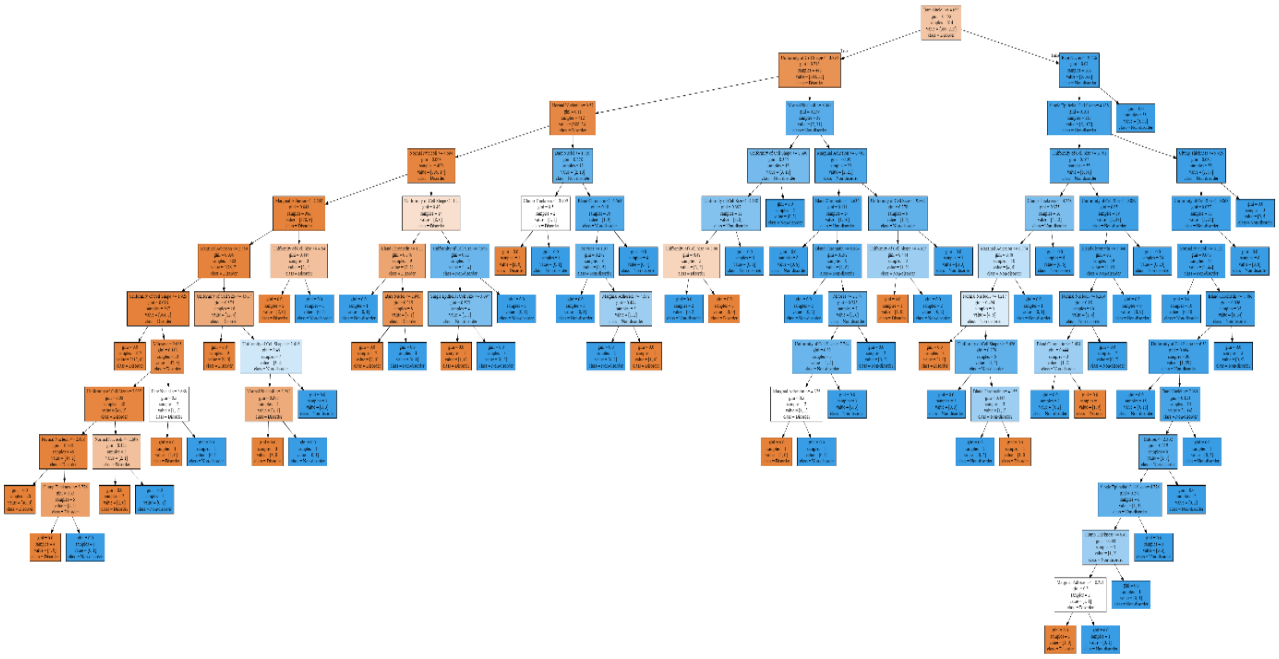


(c)

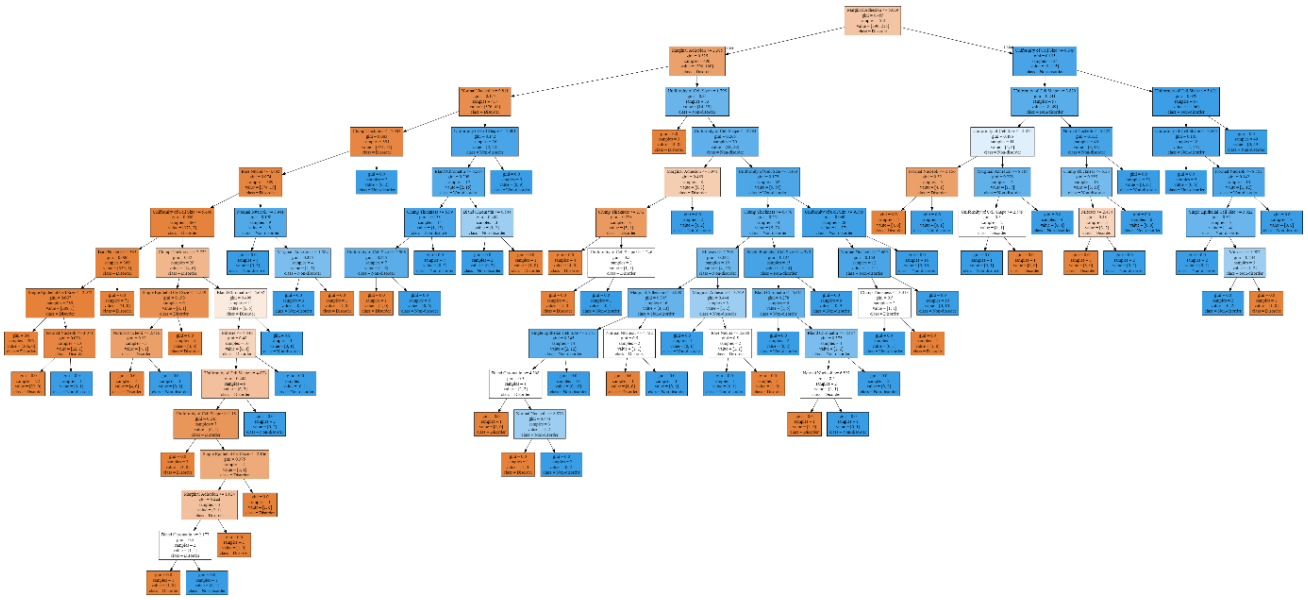


(d)

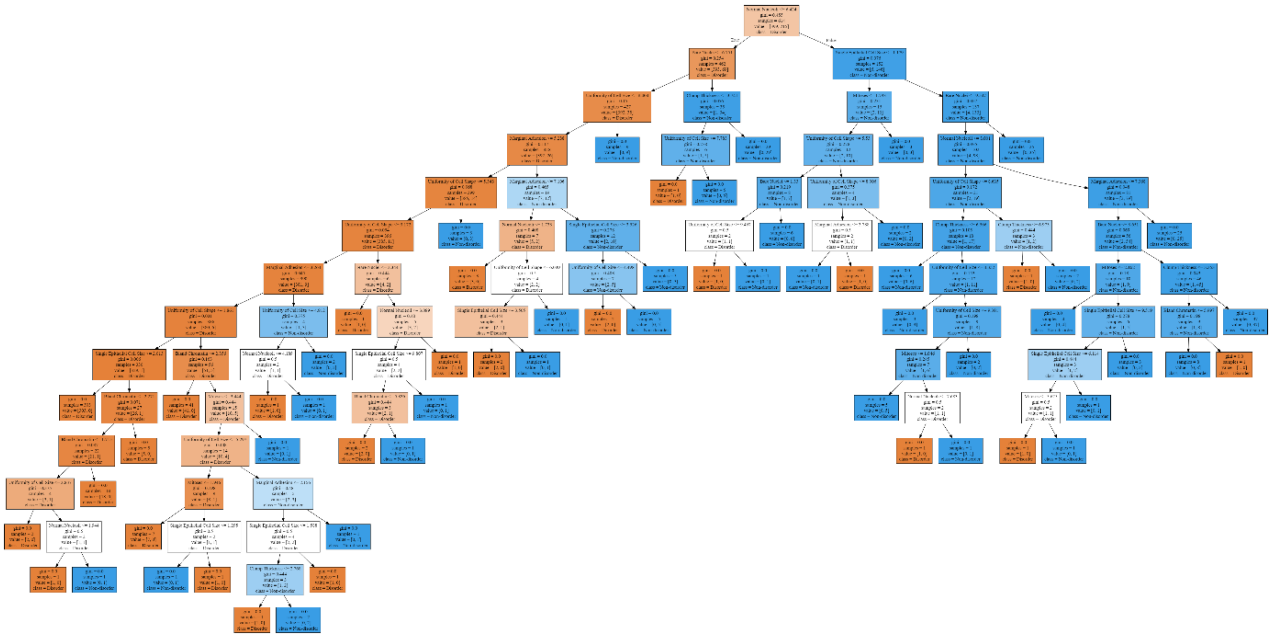
Fig. 3.2: Created trees in the structure of the proposed RF model with four trees: (a) CART#1, (b) CART#2, (c) CART#3, and (d) CART#4.



(a)



(b)



(c)

Fig. 3.3: Created trees in the structure of the developed ET model with three trees: (a) CART#1, (b) CART#2, and (c) CART#3

The decision trees created for other RF and ET models are provided in **Appendix A**. **Fig. 3.4** schematically demonstrates the RF model proposed with four CARTs for the classification of breast cancer types, according to the WBCD independent parameters. Similarly, a simple graphical representation of the created ET model with three CARTs is illustrated in **Fig. 3.5**.

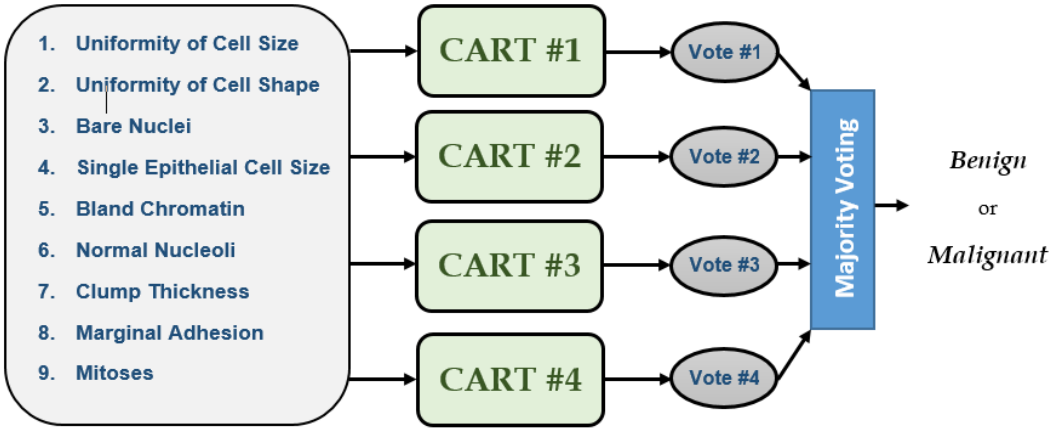


Fig. 3.4: Schematic of the proposed RF model for breast cancer classification.

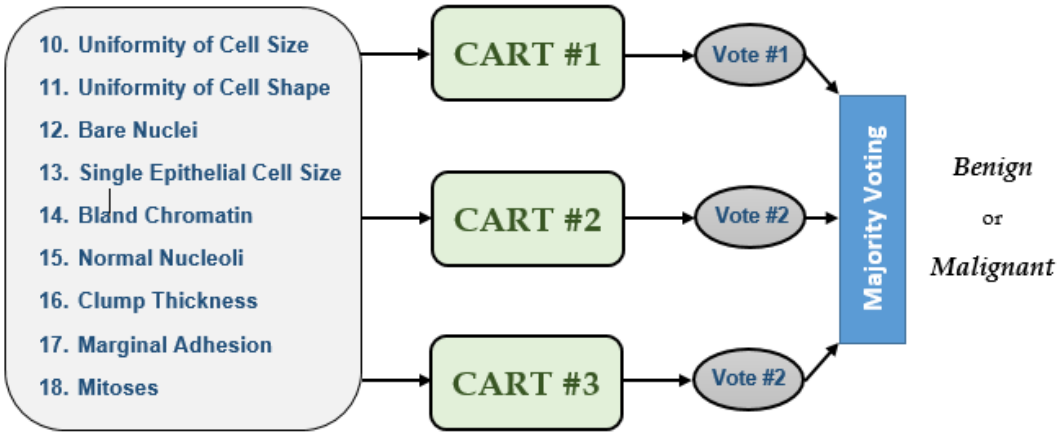


Fig. 3.5: A simple graphical representation of the proposed ET model for breast cancer classification

3.5 DISCUSSIONS

This study applies the RF and ET algorithms, as proper learning machines, to categorize the type of breast cancer. The developed RF/ET models provide a simple and efficient graphical methodology for the classification purpose. The WBCD presents the real data that includes the most vital factors (as input data) for the model development and then final decision on the correct type of the breast cancer.

Since the RF models constructed with four to ten CARTs and ET models having three to nine CARTs are able to attain the highest achievable accuracy (i.e. 100%), it is clear that no classification tool in the literature can offer such a robustness and precision. Supporting this statement, the accuracy of some available classification models in the open source literature and the accuracy of the RF and ET models proposed with three and four CARTs are listed in **Table 3.2**. As can be seen from **Table 3.2**, the classifier developed on the basis of the Naïve Bayes method [55] offers the lowest accuracy (65.27%) amongst all the studied literature models.

Table 3.2: Classification performance of the presented RF and ET models in comparison with the accuracies of the literature models.

Model	Performance		
	Accuracy	Sensitivity	Specificity
BGD-NN [49]	83.27	*	*
QN-NN [49]	98.42	*	*
LM-NN [49]	99.28	*	*
DBN-NN (conjugate gradient BP) [50]	99.59	100	99.39
DBN-NN (LM) [50]	99.68	100	99.47
RIW-BPNN (conjugate gradient BP) [50]	98.86	100	98.22
RIW-BPNN (LM) [50]	99.03	99.13	98.97
FL [51]	97.80	99.00	97.00
SVM [31]	96.49	100	86.70
k-SVM [31]	98.25	99.40	94.40
LS-SVM [53]	97.08	97.87	97.77
Dagging-RF [54]	96.49	*	*
AdaBoost-RF [54]	96.78	*	*
Multi Boosting-RF [54]	96.49	*	*
Decorate-RF [54]	96.49	*	*
Random Space-RF [54]	96.93	*	*
SVM [55]	78.45	72.00	81.00
RF (100 trees) [55]	95.64	97.00	94.00
RF (10 trees) [55]	90.13	92.00	89.00
Naïve Bayes [55]	65.27	57.00	72.00
PSO-KDE [68]	97.88	94.84	99.49
GA-KDE [68]	96.67	91.16	99.61
PCA-KNN [69]	82.30	*	*
PCA-SVM [69]	86.70	*	*
EM-PCA-CART-FL [69]	93.20	*	*
RF (this study, 4 CARTs)	100	100	100
ET (this study, 3 CARTs)	100	100	100

In addition to the robustness of the implemented RF/ET classification model, it is user-friendly and simple to understand in terms of utilization and mathematical formulation. Indeed, a physician/medical doctor can easily utilize the illustrative RF/ET model to investigate the type of breast cancer in patients without tools such as computers and access to the Internet Explorer.

The importance of the parameters included in the WBCD, namely clump thickness, uniformity of cell size, uniformity of cell shape, marginal adhesion, single epithelial cell size, bare nuclei, bland chromatin, normal nucleoli, and mitoses, in the development of the RF classification models is graphically depicted in **Fig. 3.6**.

As discussed earlier, the Gini measurements were used to calculate the feature/parameter relative importance. As can be seen from **Fig. 3.7**, each factor exhibits different importance levels while applying the RF models. However, for all the developed RF models with the number of CARTs varying from four to ten, the mitoses factor shows the lowest importance. In addition, the uniformity of cell size is the most important/influential variable in the construction of the RF models with five, six, nine, and ten CARTs. In the case of the RF models with four and eight CARTs, the most important parameter is the uniformity of cell shape. On the other hand, the bare nuclei is considered as the most influencing factor in the RF model with seven CARTs. **Fig. 3.7** depicts the same graph for the ET models. Similar to the development of the RF models, the mitoses has the lowest impact in the creation of the ET models. On the other hand, the uniformity of the cell shape is found to be the most influential parameter for the ET methodology.

Table 3.3 tabulates the average values (in percentage) of the relative importance of each independent parameter which is incorporated in the development of the RF models with four to ten CARTs.

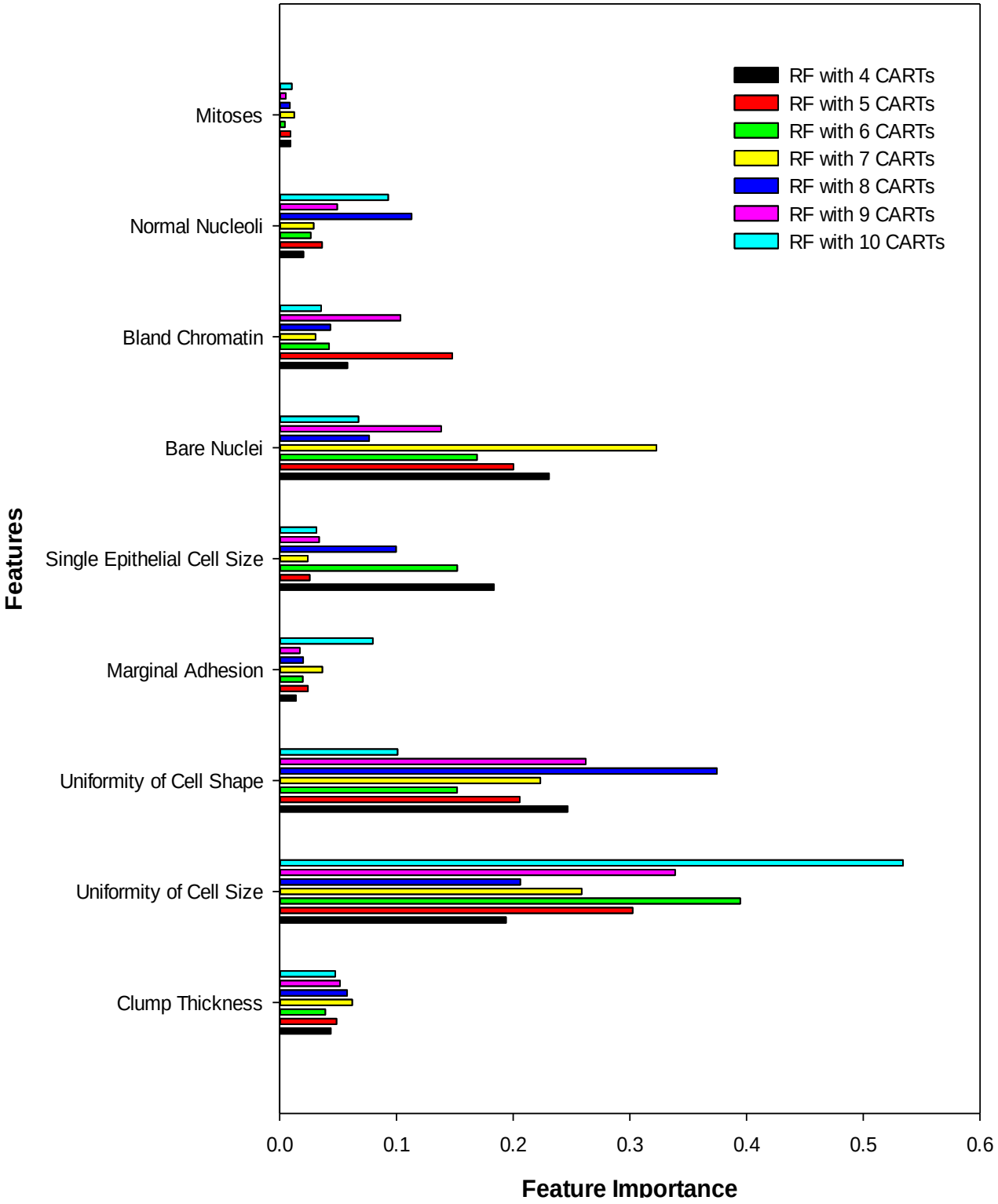


Fig. 3.6: Feature importance plot for the developed RF models.

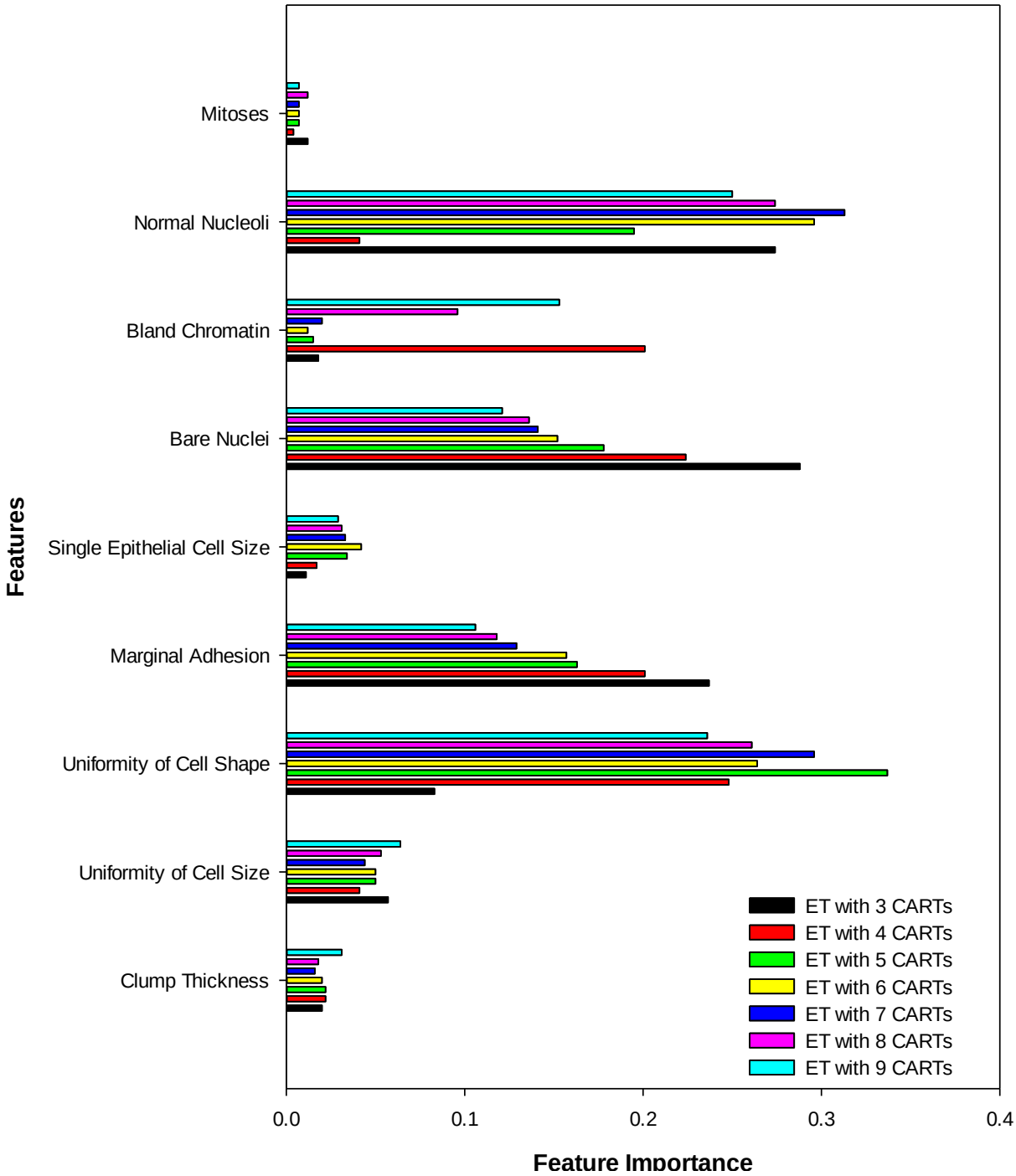


Fig. 3.7: Relative importance of the features involved in the developed ET models.

The results presented in **Table 3.3** are in a very good agreement with the feature importance obtained by the information gain technique performed on the WBCD in another study [67]. In the context of relative performance, the main difference between the results achieved from the current study and

the outcomes in the literature [67] is that it is concluded in our study that the single epithelial cell size has a higher impact on the RF model development, compared to the bland chromatin, which is different from the results of a study conducted by Hsieh et al. [65]. Similar information for the developed ET models is given in **Table 3.4**.

Table 3.3: Feature importance in average for the developed RF models with four to ten CARTs.

Feature	Rank	Importance
Uniformity of Cell Size	1	0.307901
Uniformity of Cell Shape	2	0.226715
Bare Nuclei	3	0.175527
Single Epithelial Cell Size	4	0.086836
Bland Chromatin	5	0.066213
Normal Nucleoli	6	0.049252
Clump Thickness	7	0.048068
Marginal Adhesion	8	0.030445
Mitoses	9	0.009043

Table 3.4: Feature importance in average for the proposed ET approaches with three to nine CARTs.

Feature	Rank	Importance
Uniformity of Cell Shape	1	0.246
Normal Nucleoli	2	0.235
Bare Nuclei	3	0.177
Marginal Adhesion	4	0.159
Bland Chromatin	5	0.074
Uniformity of Cell Size	6	0.051
Single Epithelial Cell Size	7	0.028
Clump Thickness	8	0.021
Mitoses	9	0.008

The developed RF and ET models are not capable of describing the relationships in the WBCD. This is due to the fact that the RF and ET methodologies are predictive modeling tools. Hence, utilization of descriptive modeling tools is recommended for future studies to detect the relationships in the breast cancer data. Another limitation of the ET and RF algorithms is that there is no universal rule to find the optimum number of trees for a classification or regression task. As a result, defining the number of weak learners is commonly conducted through trial and error procedure. It appears that development of a proper optimization strategy in this classification case is interesting to be studied by researchers.

This research offers physician/doctors effective and simple visualization tools for classification of breast cancer so that high accuracy and reliability are attained without utilization of mathematical formulas and complicated strategies. Since the developed models based on the RF/ET algorithms are data-driven models, the models can be updated, depending on the availability of more data points. Furthermore, the RF and ET methodologies can pave the way for investigation of more new features that might help in classification of cancer and other diseases/health issues. Indeed, the relative importance of each new feature, which can be obtained using these algorithms, brings new insight into understanding of the corresponding influence in the breast cancer case.

3.6 CONCLUSIONS

Development of classification models for medical diagnosis is of great interest amongst the researchers, particularly in the medicine area. This is mainly owing to the fact that classifying the medical datasets paves the way to design a more efficient medical diagnostic decision support system. It was revealed that the deterministic models existing in the literature such as ANNs, SVMs, K-NNs, fuzzy-based, and hybrid approaches offer acceptable outcomes; however, greater precision in the medicine might considerably affect the diagnosis time, cure/therapy duration, and diagnosis and therapy costs. In addition, a majority of the available tools suffer from higher complexity, lack

of optimal structure, and overfitting. Hence, the objective of the current study was to employ RF and ET to classify the breast cancer type based on the WBCD with the highest achievable precision. To attain the objective, several RF/ET classification models in conjunction with CARTs in the model structure were examined. It was found that the developed RF models with four to ten CARTs and ET models with three to nine CARTs have high potential to forecast the WBCD type with 100% accuracy in all cases. The RF/ET models with the proposed CART structures are simple to understand and appreciably efficient to categorize the WBCD so that no model can rival this classification strategy in terms of robustness, reliability, implementation speed, and precision. Hence, it is recommended to evaluate the performance of these approaches for studying the future databases on the breast cancer.

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4 DECISION TREE-BASED METHODOLOGY TO SELECT A PROPER APPROACH FOR WART TREATMENT

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PREFACE

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ABSTRACT

The human papillomaviruses (HPVs) can be responsible for various types of benign tumors called warts. Although warts can grow on all parts of the human body, common warts and plantar warts (as the most prevalent warts) grow principally on the hands and feet soles, respectively. Different treatment approaches such as cryotherapy and immunotherapy can be used to conquer the disease. However, the best healing method should be selected based on the patient circumstances. This study employs the classification and regression tree (CART) algorithm to develop accurate predictive models capable of analyzing the response of patients having common and/or plantar warts to the cryotherapy and/or immunotherapy methods. To develop a CART classifier for the cryotherapy method, independent parameters including the age and gender of patient, number of warts, type of wart, surface area of warts and the time elapsed before treatment are used. In the case of immunotherapy, in addition to the above-mentioned variables, the induration diameter of the initial test is also considered. The error analysis reveals that the implemented CART models provide the highest achievable accuracy for the application of interest. Moreover, the proposed decision tree-based models are simple to use and more reliable, in contrast to the literature models that are mainly originated from the fuzzy rule-based method. Hence, the models introduced in this study can assist both patients and physicians in saving cost/time and improving the quality of healing operation.

KEYWORDS: Warts; Cryotherapy; Immunotherapy; Classification; Decision tree; Error analysis

4.1 INTRODUCTION

As a broad category of deoxyribonucleic acid (DNA) viruses, human papillomaviruses (HPVs) can induce diseases such as cervical, anal, vulvar, and vaginal cancers. Until now, at least 150 various HPVs have been discovered in human DNA [1]. Although the HPV vaccine was introduced in 2006 as the primary prevention of HPV-related diseases, the rates of HPV vaccination are still low [2]. In addition, HPVs are responsible for benign proliferations, called warts, on the body skin [3]. It is believed that the cutaneous warts are mainly caused by some alpha-PV types (HPV2, HPV3, HPV10, HPV27, and HPV57), gamma-PV types (HPV4, HPV60, and HPV65), and mu-PV types (HPV1 and HPV63) [4-12]. A number of research studies found that the racial factor has a

significant impact on the rate of warts, since its rate is lower in African-Americans than in Caucasians [13-15]. In an annual family practice, 6% of school children and 2% of general people were known to have warts [16].

There are different types of warts including flat wart, plantar wart, common wart, filiform wart, mosaic wart, subungual wart, butcher's wart, endophytic wart, and myrmecia wart. The plantar and common warts are predominant among them [17]. Generally, the plantar warts are initiated on the foot/toes bottom and the common warts are found on the feet and hands. 70% of the cutaneous warts are known to be common warts. About 65% of untreated common warts will disappear within two years [18]. The spontaneous disappearance rate of plantar warts without treatment is between 65% and 78% [19]. Depending on the sensitivity of the patient and the anatomic location of plantar warts, they can be either painful or non-painful [20]. The medical reports show that patients, who have never had a wart, have a lower risk to be affected by warts, compared to those who have had plantar or common warts previously [21-24].

To overcome warts, there are several treatment approaches: destructive methods, immunotherapy, antimitotic drugs, and other available methodologies (e.g., duct tape, garlic extract, sinecatechins, and local hyperthermia). Surgical excision, cryotherapy, laser therapy, electro-surgery, and curettage are categorized as destructive methods. It should be mentioned that the topical chemotherapy including bichloroacetic or trichloroacetic, salicylic acid, podophyline, cantharidin, and 5-flurouracil is also considered as a conventional destructive treatment method [18]. Based on a study conducted by Kassis et al. [25], it was concluded that continuous ultrasound has no healing effect while struggling with wart disease. In the immunotherapy, the humoral and/or cellular immune responses are elicited by using drugs such as imiquimod, zinc sulfate, diphenylcyclopropenone, and cimetidine [26]. However, none of them are well-tolerated and high efficient [27]. Indeed, the therapeutic approaches can eliminate the symptoms and signs of warts. This is due to the fact that HPVs have no cure [20]. It was found that plantar warts and common warts are different in responding to the treatment [28]. Hence, it was believed that the cure for warts needs to be

individualized [18]. According to the previous studies, the success rate of the known methods applied for common wart treatment varies from 32% to 93% [29, 30].

Cryotherapy is one of the most utilized treatment methods for warts. Although cryotherapy is painful, and it has side effect, however, it is inexpensive and easy to employ. In this method, the liquid nitrogen is directly applied to warts for 10 to 20 seconds [26]. The mechanism of the cryotherapy technique is still unknown. However, it seems that the freezing operation results in local irritation and consequently, an immune response is stimulated [26]. To achieve satisfactory results, the procedure should be repeated every 2 to 3 weeks. According to a study by Bourke et al. [31], the healing rate of the cryotherapy, repeated every three weeks, for warts on hands was between 30% and 70% after three months. Other studies showed that warts treated with cryotherapy and/or salicylic acid have a 60% to 80% success rate [32-34]. This destructive approach causes blistering as it causes damage to the skin and it is painful. Moreover, there are risks of hyperpigmentation, hypopigmentation, and scarring with the cryotherapy [26].

As another wart treatment method, immunotherapy does not suffer from most disadvantages associated with the cryotherapy [17]. In this approach, a skin test antigen is injected into a lesion with the aim of inducing a T-cell-mediated, immunological response. In contrast to other available strategies for wart treatment, immunotherapy has the potential to result in a generalized immune response to the virus [35]. The key mechanism of this method is linked to a delayed-type (or type IV) hypersensitivity reaction [21]. For the first time, Lewis [36] reported the use of immunotherapy with dinitrochlorobenzene (DNCB) for common warts in 1973. Due to the mutagenic nature of DNCB, it is not utilized in the clinical setting anymore [36]. The non-mutagenic substance, known as diphencyprone (DCP), can be used for immunotherapy. Buckley et al. [37] investigated the warts treated with solutions of DCP over eight years.

For the purpose of improving the diagnosis in the medical science, implementation of machine learning and data mining approaches can be beneficial in terms of prediction accuracy and time (and

cost) aspect. Several studies reported in the literature introduce the application of predictive methods/algorithms for diagnosis and treatment selection of skin-related diseases. For example, Parikh and Shah [38] employed the support vector machine method combined with the polynomial, radial basis function, linear, t-student, and inverse multi-quadratic kernels for classification of skin diseases including fungal infection, bacterial infection, scabies, and eczema. The datasets employed in their study have been obtained from an Indian hospital. An accuracy of about 95% was attained in their study. In another research investigation, El Bachir Menai and Altayash [39] used decision tree-based method for diagnosis of erythemato-squamous disease in dermatology. Their proposed approach led to a 95% precision. In addition, there are a number of research works in the open sources that have implemented connectionist tools to investigate treatment of the melanoma (a category of skin cancers) in terms of classification and diagnosis ways [40-45].

Khozeimeh et al. [17] proposed a fuzzy rule-based methodology to study the effectiveness of cryotherapy and immunotherapy methods for treatment of common and/or plantar warts. Using the databases provided by Khozeimeh et al. [17], Akben [46] applied the ID3 algorithm to develop classification models for wart treatment selection. The developed ID3 models were then employed to create the fuzzy informative images. In another study, Khatri et al. [47] utilized the J48 algorithm in combination with the genetic programming for the same application of interest where they used the same databases as well. Guo et al. [48] employed a deep convolution neural network discriminator for differentiating between the seborrheic keratosis and flat warts. Guimarães et al. [49] utilized the fuzzy neural network method to improve the prediction capability of the expert system for the immunotherapy approach. For two commonly employed cryogens; namely nitrous oxide probes and liquid nitrogen spray, Mercer and Tyson [50] performed a mathematical modeling approach to find a relationship between the tissue freezing zone and freezing time.

Decision trees (DTs), as a type of supervised machine learning and data mining approaches, are capable of conducting the regression and/or classification problems. There are several forms of DTs including classification and regression tree (CART), ID3, C5, and C4.5 to develop a DT-based

model. In 2017, CART methodology was employed to forecast the carbon dioxide solubility in ionic liquids [51]. In another study [52], a CART-based model was presented to model the equilibrium carbon dioxide loading capacity of sodium Glycinate. In the context of classification problem, DT classification was implemented for predicting the soil drainage classes in Denmark [53].

To the best of our knowledge, there no research studies in the literature that use CART-based methods for selection of the best approach for wart removal. The primary objective of the present work is to introduce simple-to-employ and accurate decision tree (DT)-based models that can be used by physicians to select the best treatment method for common and/or plantar warts. To attain this goal, the CART algorithm is utilized for the development of efficient classifiers. Dividing the desired database iteratively, CART leads to a homogenous classification of the target/dependent parameter. One of the main advantages of the strategy proposed in this study over other algorithms is that the designed CART-based models can be visualized through an understandable manner. Indeed, there is no need for medical experts to obtain mathematical and computational information regarding the classification methodology. Hence, the visualized tree-based models can be effectively used by medical experts/doctors for the prediction purposes.

The remainder of the current research study consists of four main sections: Section 4.2 briefly describes the CART algorithm and the theory behind it. In Section 4.3, the classifier development procedure is explained. Then, the results achieved in this work are presented and discussed in Section 4.4. Finally, the conclusions are drawn in Section 4.5.

4.2 DECISION TREE LEARNING

Similar to other machine learning and intelligence approaches such as artificial neural networks, support vector machines, and adaptive neuro-fuzzy inference system, the decision trees (DTs) technique is able to solve regression and classification problems. Highlighting one important characteristic of DTs, the DT learning is known to be computationally inexpensive. Furthermore, no

assumptions are needed concerning the predictors' parameters distribution. The DTs approach is also robust in handling the missing data points [54-56].

As a decision support method, the DTs method employs a tree-like model that can be visualized. **Fig. 4.1** demonstrates a simple decision tree. The depicted tree is designed for a hypothetical analysis that has $X = (X1, X2)$ as a vector of two independent variables. As can be observed from **Fig. 4.1**, the target (dependent parameter) can be estimated through four internal nodes and five leaves. In this approach, T_i and L_i are the threshold values of the leaf. According to the decision tree presented in **Fig. 4.1**, the tree development is performed from the top to the down. At the beginning, the magnitude of X_1 is compared to a threshold value. If the value of X_1 is higher than the value of T_1, the right branch, i.e. NO, is selected for the remaining steps to obtain the final result. Otherwise, the left branch should be chosen.

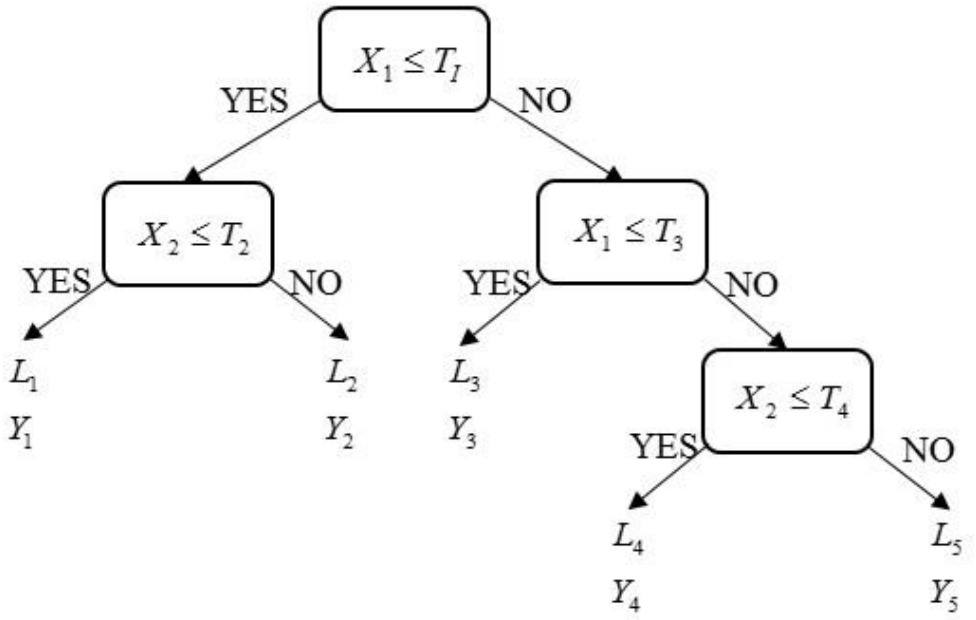

Fig. 4.1: A typical decision tree (adapted from Ref. [62]).

There are a number of algorithms suggested in the literature to develop decision tree-based regressors or classifiers. A few of the well-known algorithms include iterative Dichotomiser 3 (ID3) [55], C4.5 (developed as a successor of the ID3 learning algorithm) [57], fuzzy ID3 [58], and CART [59]. In the regression and classification applications, DTs technique offers distinct advantages. For example, the DTs model is easy to interpret and also to visualize. Indeed, compared to black-box models such as artificial neural networks, DTs models can be demonstrated in a graphical form. However, there are some disadvantages associated with DTs. One of the main drawbacks of DTs is their limitation for estimating continuous values in the context of regression analysis. Furthermore, for both classification and regression tasks, the structure of the created tree might be complicated due to the presence of many branches. The structure of DTs is highly dependent on the data introduced for modeling. In other words, variations in the dataset will change the structure of the tree. Hence, DTs methods might be variable and unstable.

Over the years, the classical CART algorithm has remained as a commonly utilized decision tree. This is mainly due to the nature of this effective methodology [51, 60]. Indeed, the CART model is fast to create, and it applies to both the quantitative and qualitative data. In this study, the CART method is used to develop tree-based classifiers for the application of interest. To develop a CART model, the recursive binary splitting is used. For regression problems, the squared residentials minimization algorithm is preferred to be employed for the splitting. In the case of classification analysis, splitting rules such as Twoing and Gini may be applied. In this research, the Gini splitting rule is utilized. To determine the importance of each feature in the collected databases, the strategy of Gini permutations/measurements is also applied. Consider that the n_k samples' fraction from $k = \{0,1\}$ category out of all the samples at the node τ is expressed as follows:

$$p_k = n_k / n \qquad (4.1)$$

In Equation (1), *p* refers to the probability of having a specific data class in a branch of the DT (node τ). The following equation presents the mathematical expression for the Gini impurity, $i(\tau)$:

$$i(\tau) = 1 - \sum_k {p_k}^2 \qquad (4.2)$$

If the node has only one single class, the equation output becomes zero that is the best value for the impurity. For a two-class problem (class 0 and class 1), $i(\tau)$ is calculated as follows [61]:

$$i(\tau) = 1 - {p_1}^2 - {p_0}^2 \qquad (4.3)$$

As the samples are separated and sent to sub-nodes τ_1 and τ_2, the Gini impurity changes. To define the reduction amount of $i(\tau)$, as a result of separating and sending the samples to sub-nodes τ_1 and τ_2 by a threshold t_θ on feature θ, the following expression can be used [61]:

$$\Delta i(\tau) = i(\tau) - p_l i(\tau_1) - p_r i(\tau_2) \qquad (4.4)$$

Depending on the applied setting (when creating a tree), the ideal strategy is to make enough branches until each branch has a Gini impurity of zero.

Conducting a proper/systematic search over all the available features at the node, the pair $\{\theta, t_\theta\}$ that leads to a maximal Δi is obtained. After this stage, the algorithm records and accumulates a decrease in $i(\tau)$ for all the nodes (individually for all features). If we have a random forest of CARTs instead of a single CART, the Gini importance is calculated using the following expression [61]:

$$I_G(\theta) = \sum_T \sum_\tau \Delta i_\theta(\tau, T) \qquad (4.5)$$

in which, $I_G(\theta)$ resembles the Gini importance and *T* denotes the number of trees in the model. The Gini importance indicates how often a specific feature θ is employed for a split, and how important its general discriminative value is for the classification analysis of the objective function.

4.3 MODEL DEVELOPMENT

4.3.1 Databases

To develop classifiers to study the applicability of the immunotherapy and cryotherapy (as wart treatment approaches), two different databases reported in the literature [17] are employed. The databanks have been gathered in Ghaem Hospital's dermatology clinic (Mashhad, Iran), in the time period of January 2013 to February 2015, from the patients affected by common and/or plantar warts. It is believed that these two categories of warts are the most widespread warts. The detailed procedure to obtain the information on the types and treatment ways of warts for the model development can be found elsewhere [17].

Using one of the databases, six vital parameters including the age and gender of the patient, number of warts, type of warts, surface area of warts, and the time elapsed before treatment are recorded to demonstrate the patient response to the cryotherapy method. The second database has seven variables to investigate the responses of the patients to the immunotherapy treatment. Both databases have six variables in common. However, the induration diameter of initial test is also considered as a key parameter for the immunotherapy approach. Eqs. (4.6) and (4.7) mathematically represent the independent variables to study the responses of patients to the cryotherapy and immunotherapy methods, respectively.

$$RESPONSE_{cryotherapy} = f\left(Age, Sex, time, warts-number, warts-type, area\right) \tag{4.6}$$

$$RESPONSE_{immunotherapy} = f\left(Age, Sex, time, warts-number, warts-type, area, induration-diameter\right) \tag{4.7}$$

More information/data such as ranges of the independent parameters existing in the databases are given in **Tables 4.1** and **4.2**.

Table 4.1: Information of patients treated with the immunotherapy strategy.

Independent parameter	Value/type
Gender	49 woman and 41 man
Age (year)	15-56
Time elapsed before treatment (month)	0-12
Number of warts	1-19
Types of warts	47 common, 22 plantar, and 21 both the common and plantar
Surface area of the warts in mm^2	6-900
Induration diameter of initial test (mm)	5-70

Table 4.2: Information/data of patients treated with the cryotherapy method.

Independent parameter	Value/type
Gender	43 woman and 47 man
Age (year)	15-67
Time elapsed before treatment (month)	0-12
Number of warts	1-12
Types of warts	54 common, 9 plantar, and 27 both the common and plantar
Surface area of the warts in mm^2	4-750

4.3.2 General step

To construct the robust classifiers based on the CART algorithm for selecting the appropriate wart treatment method, each collected database is randomly divided into two distinct categories; namely training dataset and testing dataset. Since there is no universal rule for allocations of data points to training and testing phases, the trial and error procedure can be utilized for this task. Normally, 80-

90% of the data points are used for the model training. Using 90% of the wart dataset, it is found that the CART model can provide satisfactory results.

In our study, the training dataset consists of 90% of the used databank. The remaining 10% of the data points are labelled as the test samples. This is due to the fact that the random separation of data results in a more reliable (and generalized) model. Indeed, the classifier model can be created by employing the data points allocated for the training phase of the CART model proposed in this study. Once the model was built, it can be assessed in terms of accuracy using the unseen data points, i.e. the testing dataset.

4.3.3 Classifier development

This study utilizes the CART algorithm to introduce rigorous classifiers for the proper selection of the wart treatment approach. The model development procedure is graphically represented in **Fig. 4.2**. To build a tree-based model on the foundation of the CART method, two influencing parameters including the number of features and the maximum depth of the tree need to be defined. The maximum depth of the CART refers to the maximum length among the existing paths that joins a root of the tree to a leaf.

The number of independent variables determines the number of features. The databank for the cryotherapy method consists of six independent parameters. In the case of immunotherapy method, there are seven independent parameters in the corresponding database. Since there is no universal rule to obtain the optimal CART maximum depth, a trial and error procedure is used. To start the procedure, the initial CART depth is supposed to be three. Eventually, it is found that the optimum values of the CART maximum depth are 10 and 8 for the immunotherapy and cryotherapy cases, respectively. **Fig. 4.3** demonstrates the developed CART classifier to investigate the effectiveness of the immunotherapy technique for wart treatment. The CART model proposed for the cryotherapy method is depicted in **Fig. 4.4**.

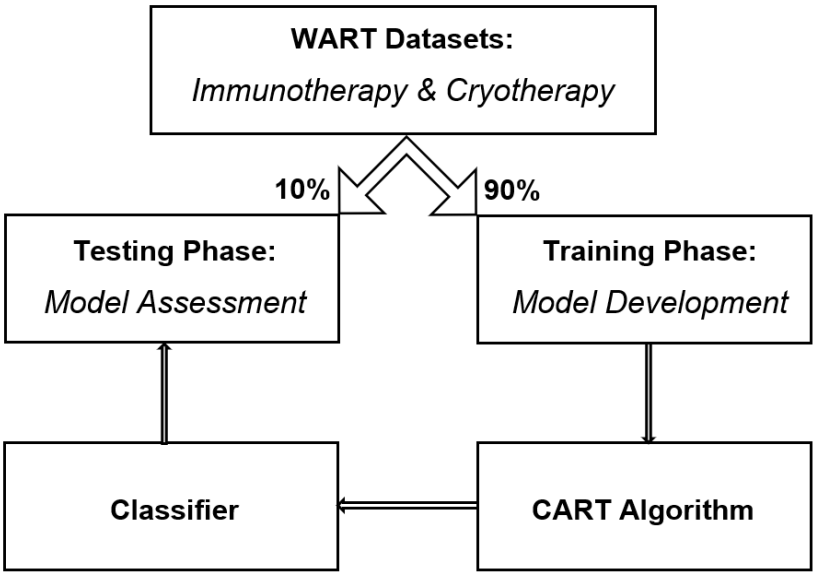

Fig. 4.2: Schematic of the procedure for model development to select the appropriate wart treatment method.

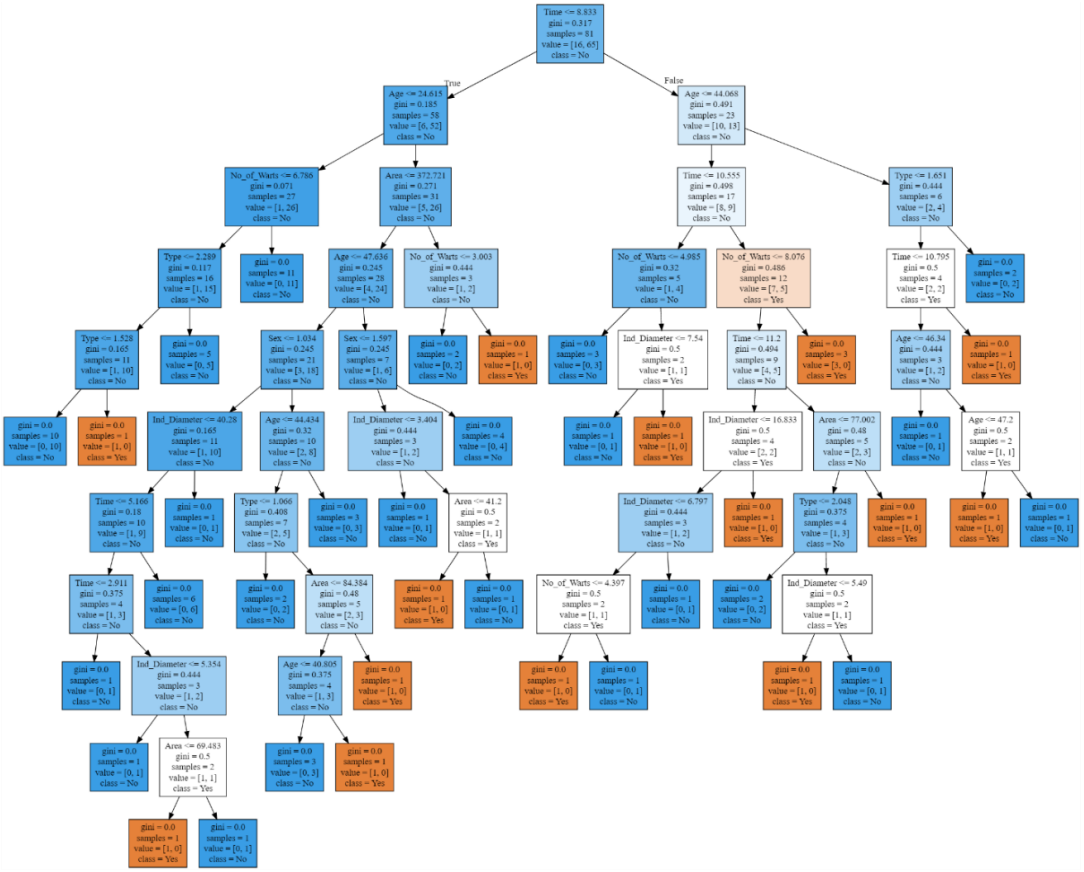

Fig. 4.3: The developed CART approach to study the effectiveness of the immunotherapy technique for wart treatment.

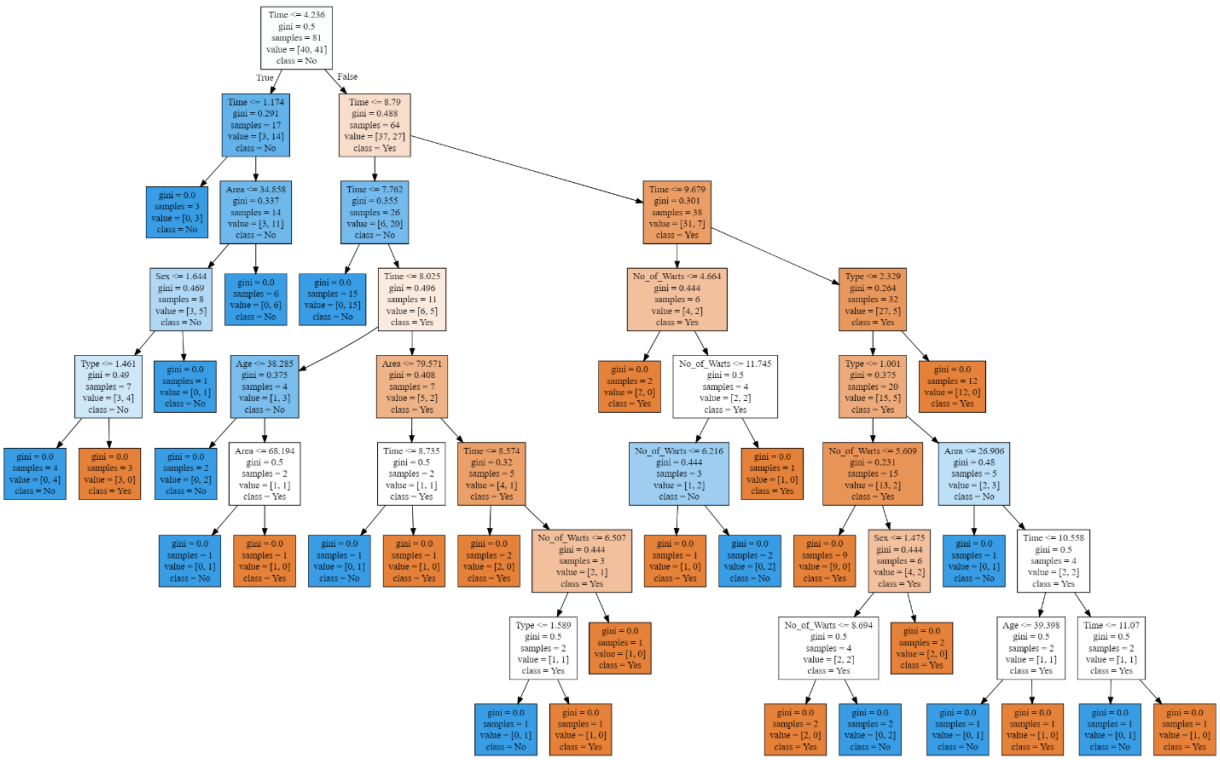

Fig. 4.4: The introduced CART model to examine the effectiveness of the cryotherapy method for wart treatment.

The digraphs of the CART models created for wart treatment through employing the cryotherapy and immunotherapy methods are provided in **Appendix B.**

4.4 RESULTS AND DISCUSSION

4.4.1 Accuracy assessment

In the case of classification problems, the accuracy only indicates the correct classification. This parameter considers equal costs for misclassification. Considering the unequal costs of decisions, the confusion matrix can be utilized to determine the specificity, sensitivity, and accuracy. Furthermore, statistical parameters such as mean squared error (MSE) and absolute average deviation (AAD) are normally used when the values of continuous variables are predicted. Most classification problems are binary variable (correct/false and yes/no.). As shown in **Figs. 4.3** and

4.4, the proposed CART classifiers provide easy-to-use and rigorous graphical models to evaluate the success of cryotherapy and immunotherapy in treating the common and/or plantar warts.

Assessing the capability of the proposed classifiers, some appropriate statistical parameters such as classification accuracy (ACC), sensitivity or true positive rate (TPR), and specificity or true negative rate (TNR) are utilized. The corresponding formulas for ACC, TPR, and TNV (in percentage) are listed below through Eqs. (4.8) to (4.10), respectively.

$$ACC = \frac{tn + tp}{tp + fp + fn + tn} \times 100 \qquad (4.8)$$

$$TPR = \frac{tp}{tp + fn} \times 100 \qquad (4.9)$$

$$TNR = \frac{tn}{tn + fp} \times 100 \qquad (4.10)$$

where *fp*, *fn*, *tn*, and *tp* stand for the false positive, false negative, true negative, and true positive, respectively.

The statistical analysis reveals that the outcomes obtained from the presented CART models are in excellent agreement with the existing real data. Indeed, both the CART models developed for the cryotherapy and immunotherapy methods are able to forecast the patient response to the treatment without any error. In other words, the values of ACC, TPR, and TNV for the proposed CART models are equal to 100% for both the training and testing phases.

4.4.2 Comparison with other available techniques

In 2017, Khozeimeh et al. [17] employed a fuzzy rule-based framework to select the proper method for wart treatment. Recently, Akben [46] and Khatri et al. [47] utilized DT-based algorithms for the development of classification models with a capability for selecting the best approach for wart

treatment. Furthermore, Khatri et al. [47] evaluated the classification capability of several methods including support vector machine (SVM), k-nearest neighbors (KNN), random forest (RF), naïve Bayes (NB), logistic regression (LR), linear discriminant (LD), bagged trees (BaT), and boosted trees (BoT). It should be mentioned that all the previous studies discussed in the current research work have used the same databanks to introduce the classification strategies. To evaluate the robustness of the model proposed in this study for selecting the most effective wart treatment technique, the previous research investigations that employed the same databases, but different predictive approaches, are chosen for the comparison purposes.

For the immunotherapy technique, **Table 4.3** summarizes a comparison between the proposed CART model and the available models (in the literature) in terms of sensitivity (TPR) and specificity (TNV) as well as the accuracy. As it is evident from **Table 4.3**, the decision tree-based models outperform the previous models introduced for the immunotherapy case. In addition, the BoT and LD models exhibit the weakest results with an accuracy rate of 78.9% for the immunotherapy scenario.

Fig. 4.5 illustrates a graphical method to compare the accuracies of our new CART models and the models available in the open sources.

Correspondingly, **Table 4.4** compares the classification performance of the introduced CART model for the cryotherapy case to that of the above-mentioned literature models. Similar to the immunotherapy case, the results tabulated in **Table 4.4** exhibit the superiority of the suggested CART model over the previous models for the cryotherapy treatment methodology.

Table 4.3: Comparison between the performance of the proposed CART model and the literature models for immunotherapy case based on statistical analysis.

Model	Assessment parameter		
	ACC	TPR	TNR
CART (this work)	100	100	100
Fuzzy rule-based [17]	83.3	87.0	71.0
J48 [47]	82.2	82.2	56.7
GA-J48 [47]	96.7	96.7	91.4
ID3 [46]	90.0	97.2	63.2
SVM [46]	87.8	*	*
KNN [46]	87.8	*	*
LR [46]	83.3	*	*
LD [46]	78.9	*	*
NB [46]	87.8	*	*
RF [46]	80.0	*	*
BaT [46]	80.0	*	*
BoT [46]	78.9	*	*

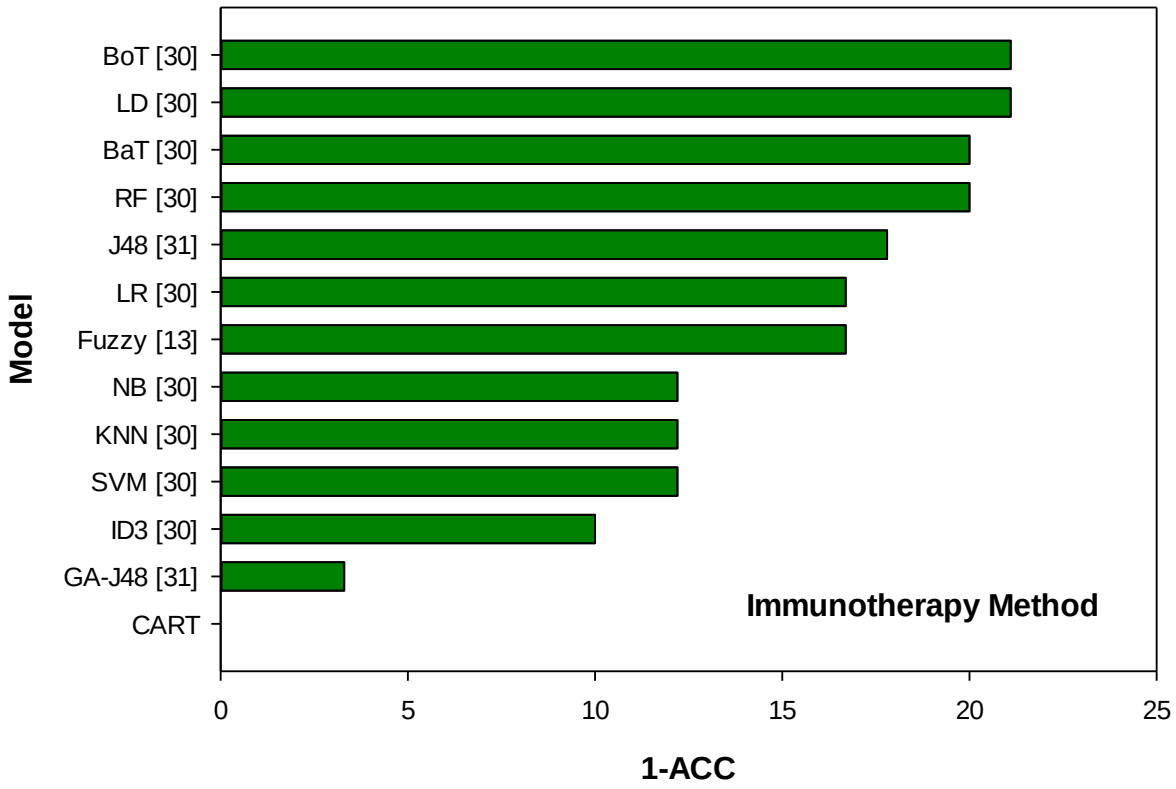

Fig. 4.5: Graphical comparison of the proposed CART model with the literature models for the immunotherapy method.

Table 4.4: Values of statistical parameters for the proposed CART model and the literature models for cryotherapy case based on comparison between predictions and real data.

Model	Assessment parameter		
	ACC	TPR	TNR
CART (this work)	100	100	100
Fuzzy rule-based [17]	80.0	82.0	77.0
J48 [47]	93.3	93.3	93.9
GA-J48 [47]	98.9	98.9	87.0
ID3 [46]	94.4	89.6	100
SVM [46]	90.0	*	*
KNN [46]	88.9	*	*
LR [46]	86.7	*	*
LD [46]	87.8	*	*
NB [46]	85.6	*	*
RF [46]	92.2	*	*
BaT [46]	92.2	*	*
BoT [46]	82.2	*	*

For the cryotherapy case, the fuzzy rule-based strategy [17] achieved 80% accuracy, which is the lowest amongst the available literature models. The performance of the literature models as well as our CART model in terms of precision is graphically presented in **Fig. 4.6**.

Comparing the results of the proposed CART models with the outcomes of the models suggested by Khozeimeh et al. [17], Akben [46], and Khatri et al. [47] reveals the supremacy of the decision tree-based techniques over the literature models for selection of the best approach for wart treatment. Beside the accuracy, the CART models provide a simple-to-use framework to select the proper treatment method without any calculator or computer assistance, while the fuzzy rule-based models appear to be appreciably sophisticated where the computational procedure might be complicated. As a result, the predictive models proposed in this study is more reliable and applicable than other literature models for medical experts. In other words, since there is no need to have knowledge and

theoretical background about mathematical expressions or machine learning fundamentals, the proposed tree-based models can be simply utilized by medical experts/doctors before implementing a treatment procedure. Generally, employing this type of classification techniques in the health and medical sectors leads to higher success rates in diagnosis and treatment of various diseases so that they decrease the associated expenses and time required for the corresponding medical operations.

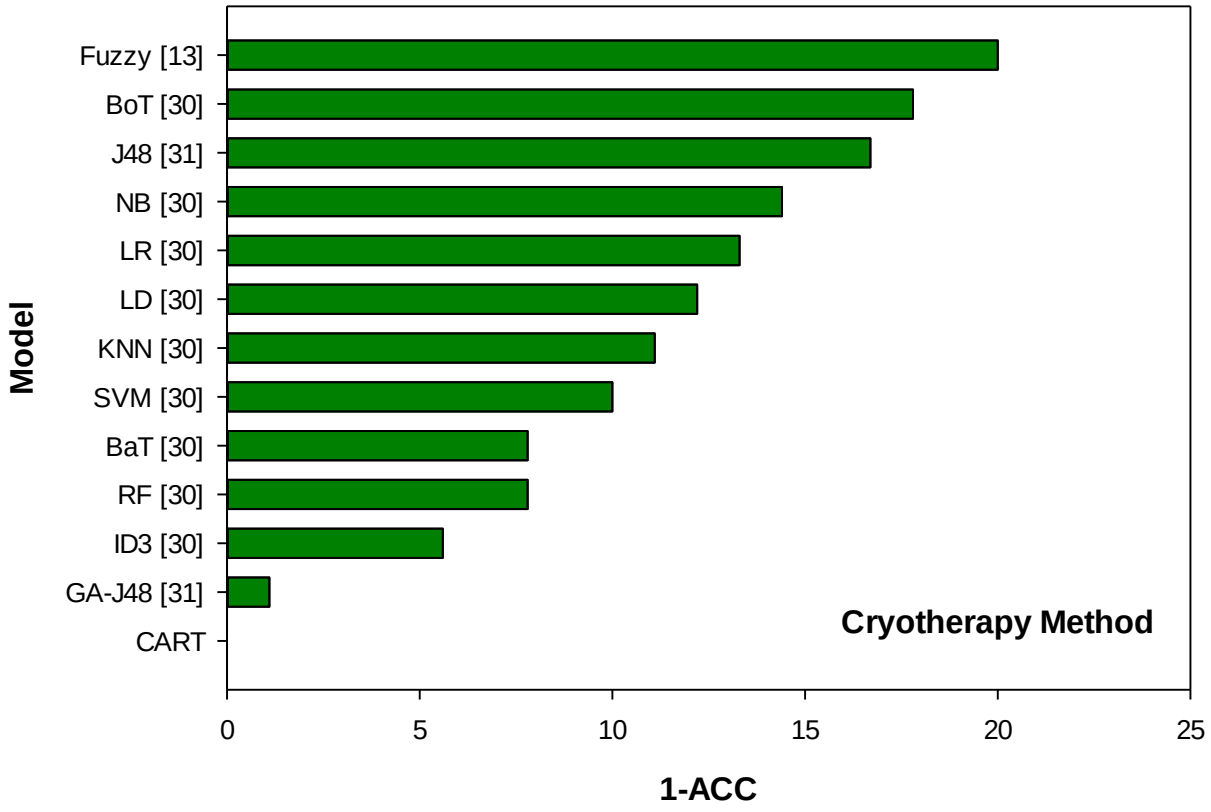

Fig. 4.6: Comparison of performance of the proposed CART model with that of the previous models for the cryotherapy scenario.

4.4.3 Feature importance

The importance of each independent parameter involved in the development of the CART classifiers for the immunotherapy dataset is depicted in **Fig. 4.7**.

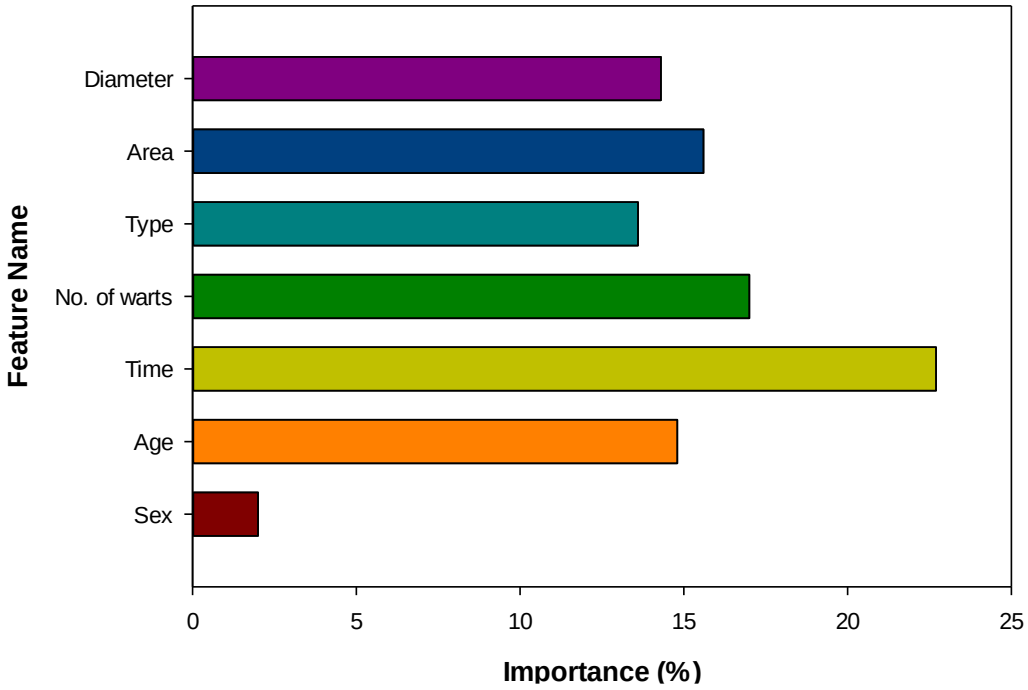

Fig. 4.7: Relative significance of the features involved in the CART model for immunotherapy approach.

As seen in **Fig. 4.7**, the most important feature, to realize whether the immunotherapy is a proper treatment method or not, is the time elapsed before performing the treatment. This feature has 22.7% importance in the construction of the CART model. The outcome of the study conducted by Khozeimeh et al. [17] is in agreement with this research finding as Khozeimeh et al. [17] concluded that the time elapsed before accomplishing the immunotherapy has the highest effectiveness. Also, gender of the patient, with just 2% influence on the CART structure development has the least significance among the contributing factors. Although the literature [17] claimed that the gender of patient has a low effectiveness in immunotherapy case, the lowest impact is associated with the number of warts based on our research study. Other features including the induration diameter of initial test, age of the patient, number of warts, type of warts, and the surface area of the warts have almost the same significance in the decision tree creation process.

Fig. 4.8 describes the relative importance of the features employed to develop the CART model for assessment of the effectiveness of the cryotherapy method. Similar to the immunotherapy case, the most important variable in the CART development process is the time elapsed before starting a treatment. It is worth noting that this parameter is more important than other features of the database all together such that it has a 55.77% significance in the CART model development for the cryotherapy method. However, the lowest importance for this database belongs to the gender of the patient. The results obtained by Khozeimeh et al. [17] showed that the gender has the minimum importance when the patient is treated by the cryotherapy, which is the same as the finding of the current study. However, based on the methodology employed by Khozeimeh et al. [17], the highest relative rank was given to the age of patients, which is in contradiction with the outcome of the present study.

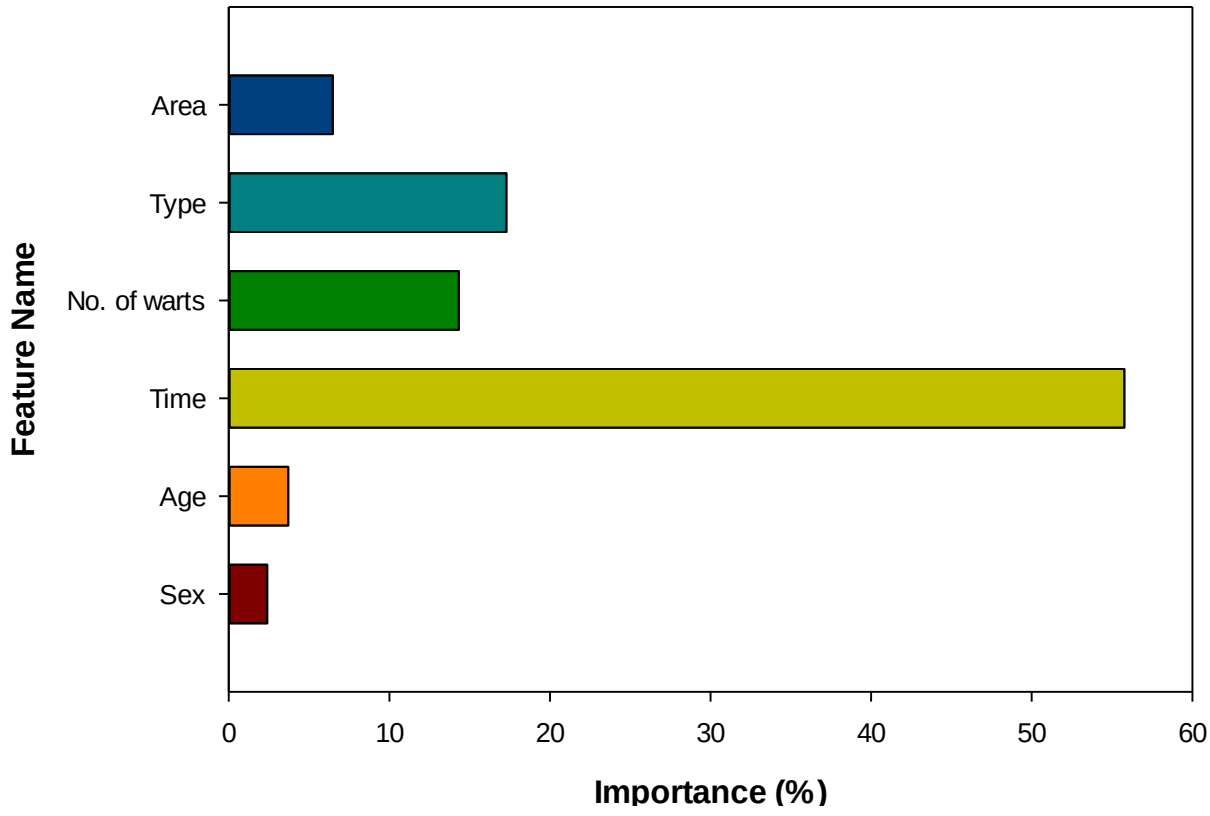

Fig. 4.8: Feature importance plot of the CART model suggested for cryotherapy method.

4.5 CONCLUSIONS

In the current, CART methodology is employed to develop robust classifiers to choose the proper treatment approach (cryotherapy or immunotherapy) for common and/or plantar warts. The performance of the developed tree-based classifiers is compared to that of the methodologies available in the literature in terms of reliability and prediction accuracy. Outcomes of the introduced CART models reveal an excellent performance for both cryotherapy and immunotherapy approaches so that the ACC, TPR, and TNR are found to be 100%. On the other hand, the literature models for the cryotherapy case lead to ACC, TPR, and TNR ranging from 80.0% to 98.9%, 82.0% to 98.9%, and 77.0% to 100%, respectively. For the immunotherapy case, the magnitudes of ACC, TPR, and TNR are between 78.9%-96.7%, 82.2%-97.2%, and 56.7-91.4%, correspondingly. Furthermore, the proposed models appear in a graphical form and can be easily employed in an understandable manner. Hence, it can be concluded that no model can rival the proposed CART models in terms of both accuracy and simplicity of implementation. By obtaining further information from various groups of patients, it is possible to present more efficient (and generalized) decision tree-based models that can be more practical for different cases. It is recommended to incorporate effective hybrid and ensemble methodologies (e.g., genetic algorithm and particle swarm optimization) into the CART algorithm for future studies. Implementation of hybrid/ensemble methods might further simplify (and improve) the structure of the tree-based models developed for wart treatment.

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5 DECISION TREE-BASED DIAGNOSIS OF CORONARY ARTERY DISEASE: CART MODEL

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PREFACE

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ABSTRACT

Background and Objective: As the most common cardiovascular defect, coronary artery disease (CAD), also called ischemic heart disease, is one of the substantial causes of death globally. Several diagnosis approaches such as baseline electrocardiography, echocardiography, magnetic resonance imaging, and coronary angiography are suggested for screening the suspected patients that may suffer from CAD. However, applying such methods may have health side effects and/or expensive costs.

Methods: As an alternative to the available diagnosis tools/methods, this research involves a decision tree learning algorithm called classification and regression tree (CART) for a simple and reliable diagnosis of CAD. Several CART models are developed based on the recently CAD dataset published in the literature.

Results: Utilizing all the features of the dataset (55 independent parameters), it was found that only 40 independent parameters influence the CAD diagnosis and consequently development of the predictive model. Based on the feature importance obtained from the first CART model, three new CART models are then developed using 18, 10, and 5 selected features. Except for the five-feature CART model, the outcomes of developed CART models demonstrate the maximum achievable accuracy, sensitivity, and specificity for CAD diagnosis (100%), while comparing the predictions with the reported targets. The error analysis reveals that the literature models including sequential minimal optimization (SMO), bagging SMO, Naïve Bayes (NB), artificial neural network (ANN), C4.5, J48, Bagging, and ANN in conjunction with the genetic algorithm (GA) do not outperform the CART methodology in classifying patients as normal or CAD.

Conclusions: Hence, the robustness of the tree-based algorithm in accurate and fast predictions is confirmed, implying the proposed classification technique can be successfully utilized to develop a coherent decision-making system for the CAD diagnosis.

***KEYWORDS**:* coronary artery disease; classification; decision tree; error analysis; Classification and Regression Tree

5.1 INTRODUCTION

Coronary artery disease (CAD) appears to be the most common cardiovascular defect; heart disease is a leading cause of global deaths. A study showed that CAD is responsible for the death of one-third of women, regardless of the ethnicity or race [1]. According to the World Health Organization (WHO) [2], CAD is the world's biggest killer amongst the top ten death causes including CAD, stroke, chronic obstructive pulmonary disease, lower respiratory infections, Alzheimer disease and

other dementias, diabetes mellitus, road injury, diarrhoeal diseases, tuberculosis and trachea, bronchus, and lung cancers. Although the heart disease management has drastically changed in recent decades [3, 4], individuals with stable CAD are still prone to a significant adverse cardiovascular incident [5-7]. According to a study [8], more than 6% of the adult population in the United States are suffering from CAD. Furthermore, it has been estimated that the clinical CAD will be the issue of approximately one-third of middle-aged women and half of the middle-aged men across the United States [8].

Atherosclerosis, a condition in which plaque builds up inside the arteries supply oxygen-rich blood to the heart, characterizes CAD. The plaque formed over the years is responsible for narrowing the coronary artery lumen and, consequently, limiting the blood flow through the artery. The chest pains in the form of pressure sensation or squeezing can be a symptom of CAD. However, several patients with CAD show no symptoms of the disease [9]. To screen the patients, guideline recommendations are employed; the proposed tips are currently documented by the American Association of Clinical Endocrinologists (AACE), American College of Cardiology/American Heart Association (ACC/AHA), and US Preventive Services Task Force (USPSTF) [10-12].

The 2004 INTERHEART study [13] defined nine modifiable risk factors that are correlated with CAD. These factors include smoking, hypertension, abdominal obesity, diabetes, stress and depression, regular alcohol consumption, daily consumption of vegetables and fruits, dyslipidemia, and regular physical activity. The majority of the risk factors are similar in women and men. However, compared to men, women are found to have a stronger risk factor profile at younger ages. Men, on the other hand, tend to have better health conditions at older ages [14]. Indeed, at first CAD manifestation, women are approximately ten years older than men [15]. However, smoking, diabetes or premature menopause throw this advantage away [14]. The race is known to be another risk factor for CAD. For example, some studies revealed that CAD rate among Asian Indians is higher than that of other ethnics [14, 16]. Family history is also associated with the risk of CAD. Based on a

research investigation [17], CAD family history in a sister has 12-fold higher risk versus 3-fold for a parent and 6-fold for a brother.

For patients with known or suspected CAD, conventional invasive coronary angiography is found to be the gold standard for diagnosis purposes [18]. However, this approach is time consuming, invasive, and expensive. Its invasiveness nature may cause a degree of discomfort for some patients, since this method usually needs a short stay at the hospital [19]. Moreover, this modality has a small but considerable complication rate [20]. Electron-beam computed tomography (EBCT) has paved the way for morphological evaluation of cardiac structures. This is owing to the high temporal resolution of EBCT and the use of prospective electro-cardiographic triggering as well. However, due to the inferior spatial resolution of the EBCT approach, it was not considered as a proper strategy for identifying the presence of coronary stenosis [19]. The introduction of computed tomography (CT) angiography led to substantial improvements in the detection of CAD as well as the assessment of the heart function in different conditions [21-23].

There are some prevention ways to deal with CAD. These approaches can be divided into two categories, namely primary prevention and secondary prevention. Indeed, primary prevention can be defined as the treatments or modification of risk factors that are proven to avert the first or initial coronary event [24]. A common example of this prevention category is using lipid-lowering agents to avoid the occurrence of the first myocardial infraction [25]. On the other hand, the treatment modalities that are initiated after the first event for the prevention of subsequent outcomes are known as secondary prevention strategies. For example, utilization of beta-blockers after myocardial infarction, for new events reduction, belongs to this classification [26].

Studies showed that physical activity reduces the CAD risk. The role of physical activity in both primary and secondary prevention is studied in the literature. For example, in the case of primary prevention, the protective function of working out was declared in the United States for a large cohort of longshoremen [24]. For the secondary prevention, the Clinical Practice Guidelines for

Cardiac Rehabilitation [27] indicated that the improvement extent is dependent on different factors, including duration, intensity and frequency of activity, and the training time interval. The concerns regarding regular aerobic exercise are addressed in some research investigations. It was revealed that regular moderate-intensity exercise decreases the cardiac mortality risk, and even with vigorous exercise, the sudden death incidence is low [28, 29]. However, the risk of myocardial infarction increases with a high-intensity and vigorous exercise [24].

In addition to the traditional and routine screening approaches to detect CAD, some predictive models have been developed based on different machine learning (ML) and data mining methodologies. This study is intended to employ the decision tree learning algorithm, particularly the CART, for the diagnosis of CAD. To the best of our knowledge, this is the first work on the application of CART to study the Z-Alizadeh Sani CAD dataset for diagnosis/classification purposes. Furthermore, we compare the outcomes of our new models with the results of the previously used models, developed based on various methodologies such as ANN and support vector machine (SVM). Furthermore, we develop several CART models based on different inputs; the inputs are not selected randomly. Indeed, we introduce a new CART model through employing all the inputs existing in the Z-Alizadeh Sani CAD dataset. Based on the Gini index, we then define the relative importance of each independent parameter for the development of the CART model. Finally, we obtain two more CART-based models using the independent parameters, which are detected (recognized) as important parameters. Further highlighting the novelty of this research, the contributions of the work is as follows: a) Utilization of the CART strategy for CAD diagnosis using Z-Alizadeh Sani CAD dataset for the first time, b) Selection of vital input parameters and determination of relative importance of inputs, c) Design of the optimal CART model in terms of structure/topology and parameters values, d) Proper data mining for training and testing phases, e) Systematic statistical analysis for performance evaluation of various classification tools, and f) Higher accuracy and simpler (and more understandable) outcomes of the CART approach, compared to the previous techniques applied to the dataset.

In fact, the CART results would help physicians and health scientists to better understand the relationships between different parameters and CAD.

According to the literature, several connectionist and predictive/deterministic methods are currently being used in various science, health, and engineering disciplines for different purposes, particularly when a large amount of data is available. In all cases, selection and application of proper techniques, data mining/management, choosing vital important input data, tuning the parameters of deterministic or classification models based on the selected methods, finding the relative importance of input parameters, results and statistical analysis, and making proper decisions are among the novelties of research works.

After the introduction section, a review of the published works in the literature on the classification of CAD using various ML and data mining approaches is provided. Section 5.3 presents an overview of the CART methodology for the classification task. Modeling procedure for the application of interest is addressed in detail in Section 5.4. Section 5.5 includes the findings as well as a discussion about the modeling results. Finally, the main conclusions are highlighted.

5.2 RELEVANT STUDIES

In 2017, Xu et al. [30] employed the multivariate logistic regression to detect the correlation between CAD and defined risk factors such as smoking status, angina, age, sex, hypertension, diabetes, serum creatinine, and dyslipidemia. The developed model was then used to differentiate non-CAD from CAD in the test sample. The data required for modeling purpose were gathered by studying 8297 patients, ranging between 19 to 90 years old, in the north and south of China between 2008 and 2014. After excluding the patients with incomplete data, 4678 male patients and 2682 female patients, both symptomatic and asymptomatic cases, were selected/utilized.

The following expression represents the model developed by Xu et al. [30] for CAD prediction:

$$p = \frac{\exp f(x)}{1 + \exp f(x)} \quad (5.1)$$

where *p* is the probability of CAD and $f(x)$ refers to the discriminant vector. Eq. (5.2) is used to calculate the value of $f(x)$as follows:

$$f(x) = A_0 + \sum_{i=1}^{n} \beta_i x_i \quad (5.2)$$

in which, β_i and x_i denote the regression constants and risk factors, respectively; and A_0 is the intercept.

The above-mentioned model presented a specificity of 0.709 and a sensitivity of 0.658, which is fairly acceptable, but not accurate enough. Although this model is simple to use based on the original work described by the researchers, it is a simplified model that does not consider other vital risk factors including family history and body mass index.

Davari Dolatabadi et al. [31] implemented the support vector machine (SVM) algorithm to present an automatic CAD diagnosis model. In their study, they employed the signal extracted from electrocardiogram (ECG) as well as heart rate variability (HRV). The used data points were obtained from the recording of 86 lengthy ECG of 80 individuals, in which 46 cases were men aged between 44 and 85, and 29 cases were women aged between 23 and 87 years. Finally, they only selected 23 cases, who suffered from CAD, from this databank. For the normal group, they used 23 normal individuals that were obtained from 24-hour Holter monitor recordings of 30 healthy men and 24 healthy women (aged from 29 to 76). With the aim of reducing the features' dimension, the authors applied a method called principal component analysis (PCA). The proposed SVM classifier was able to offer a sensitivity, specificity, and accuracy of 98.43%, 100%, and 99.2%, respectively.

Utilizing a simulated dataset of heart disease containing 1000 patient records, Ilayaraja and Meyyappan [32] applied a data mining algorithm for prediction of the heart diseases risk via

Frequent Itemsets. Chest pain, swelling of the ankles and feet, swelling in legs, shortness of breath, fatigue, fever, fluttering in the chest, swelling in the abdomen, changes in the heart rhythm, racing heartbeat, slow heartbeat, dry or persistent cough, lightheadedness, fainting or near fainting, skin rashes or unusual spots, breathlessness with exertion or at the rest, irregular heartbeats (rapid, pounding or fluttering), pain in the neck, jaw, throat, upper abdomen or back pain, numbness and weakness or coldness in the legs or arms (if the blood vessels are narrowed) are the attributes of the used dataset.

Tan et al. [33] implemented the convolutional neural network (CNN) with long short-term memory (LSTM) model for the CAD diagnosis through employing ECG signals. The presented stacked CNN-LSTM model is fully automatic. The CNN method was also utilized by Acharya et al. [34] for automated detection of CAD by applying different durations of ECG segments. In another research investigation, Giri et al. [35] used heart rate signals to develop a methodology for the automatic detection of CAD and normal conditions. They employed several approaches such as PCA, SVM, independent component analysis (ICA), linear discriminant analysis (LDA), Gaussian mixture model (GMM), k-nearest neighbor (KNN), and probabilistic neural network (PNN). Acharya et al. [36] employed CWT-based contourlet and shearlet transforms of ECG signals for the detection of CAD, congestive heart failure (CHA), and myocardial infarction. Higher-order statistics and spectra (HOS) and flexible analytic wavelet transform (FAWT) methods were also investigated in other studies [37, 38].

In a research study conducted by Sood et al. [39], the heart rate signals were processed using the empirical mode decomposition (EMD) technique. To classify CAD and normal subjects, the researchers extracted several features. In addition to EMD, Acharya et al. [40] employed various methods including Poincare plots, recurrence quantification analysis (RQA) parameters, Shannon entropy, approximate entropy, sample Entropy, higher-order spectra methods, detrended fluctuation analysis (DFA), cumulants, and correlation dimension for the application of interest.

For the prediction of CAD, Forssen et al. [41] employed metabolomic data along with several approaches namely PCA regression, L1 regression, and random forest. The required data for modeling were collected from the Clinical Cohorts based on the Coronary Disease Collaboration study in some UK hospitals. Using a nuclear magnetic resonance (NMR) technique, they quantified 256 metabolites for each individual. The dataset was randomly divided into two subsets: training (75%) and testing (25%). The presented models provided sensitivities between 88.2% and 98.4%. However, the obtained values for specificity were between 2.6% and 33.9%.

There are some publications in the literature on the application of various machine learning and data mining strategies in the development of predictive models with the aid of a publicly available database known as UCI Cleveland dataset [42] for CAD diagnosis. The Cleveland dataset contains 303 cases of patient data points, in which 6 of them are incomplete. Hence, these data were omitted from the dataset before the modeling process. Each set of data points has 13 independent attributes including age, gender, chest pain type, serum cholesterol, resting blood pressure, fasting blood sugar, resting electrocardiographic results, exercise-induced angina, maximum achieved heart rate, ST depression induced by exercise relative to rest, the heart status, number of major vessels, and the slope of the peak exercise ST segment. The dependent parameter is the diagnosis of heart disease that is either normal or sick (three different types). For example, Purushottam et al. [43] compared the performance of several methods such as SVM, C4.5, multi-layer perceptron (MLP) ANN, and radial basis function (RBF) ANN in classifying the Cleveland dataset.

Nguyen et al. [44] proposed the interval type-2 fuzzy logic system (IT2FLS) and wavelet transformation (WT) for Cleveland dataset classification. They compared the results of the proposed model with the outputs of other models including SVM, probabilistic neural network (PNN), adaptive neuro-fuzzy inference system (ANFIS), and fuzzy ARTMAP. Based on the performance metrics, the IT2FLS in conjunction with wavelets provided the best predictions with accuracy, sensitivity, and specificity of around 80%, 84%, and 77%, respectively.

In another work, Uyar et al. [45] employed the Cleveland dataset for developing a diagnosis model. The approach introduced by Uyar et al. [45] is based on recurrent fuzzy neural networks (RFNNs). The authors employed GA for training the RFNN. 85% of the data points were used for the training phase and the remaining 15% was allocated for the testing phase. The presented GA-RFNN model led to a sensitivity, specificity, and accuracy of 97.74%, 95.73%, and 96.63%, respectively. Other works in this research area can be found elsewhere [46-50].

In 2013, a new dataset for heart disease, known as called Z-Alizadeh Sani dataset, was published [51]. Alizadehsani et al. [51] utilized several methods namely ANN, SMO, NB, and bagging algorithms to analyze the Z-Alizadeh Sani dataset. In addition to the above-mentioned algorithms, they also used feature creation and feature selection methods to assess the results. It was found that the performances of the classification algorithms are better when both the feature creation and feature selection techniques are used.

In another study by Alizadehsani et al. [52], Z-Alizadeh Sani dataset was divided into the train (90%) and test (10%) datasets. Then, the information gain and SVM were used for feature analysis and feature selection. For the classification purpose, the researchers employed the SVM methodology in combination with several kernel functions including RBF, sigmoid, linear, and polynomial.

Utilizing the ANN and GA modeling techniques, Arabasadi et al. [53] classified the Z-Alizadeh Sani dataset in 2017. The attained magnitudes of sensitivity, specificity, and accuracy for the GA-ANN were 97%, 92% and 93.85%, respectively. On the other hand, the ANN model classified the dataset with 84.62% accuracy, 86% sensitivity, and 83% specificity. Hence, the classification capability of the presented hybrid model of GA-ANN is considerably higher than the developed ANN model. Performance of cost-sensitive techniques along with the Naïve Bayes, SVM, SMO, C4.5, and KNN strategies in CAD classification was also evaluated in a research study by Alizadehsani et al. [54]. To achieve more accurate outputs in the context of CAD classification, Alizadehsani et al. [55]

proposed a machine learning-based model to detect left circumflex, left anterior descending, and right coronary artery.

Acharya et al. [56] compared the performance of discrete wavelet transform (DWT), empirical mode decomposition (EMD), and discrete cosine transform (DCT) in the detection of CAD and myocardial infarction. Alkeshoush et al. [57] evaluated the potential of the PSO algorithm in the diagnosis of heart disease. The diagnostic performance of cardiac phase-space tomography analysis was examined by Stuckey et al. [58]. In another study, Steele et al. [59] found that ML methods in electronic health records are better than conventional survival methods for forecasting patient mortality in CAD. Recently, Johnson et al. [60] employed ML approaches for the scoring of CAD characteristics on coronary CT angiograms. In 2019, Alizadehsani et al. [61] conducted a review of ML-based studies for CAD prediction.

5.3 CART METHODOLOGY

Among the available learning algorithms for decision trees such as Iterative Dichotomiser 3 (ID3) [62], C4.5 [63], successor of the ID3 learning algorithm, fuzzy ID3 [64] and CART [65], the CART strategy is known to be one of the most successful techniques [65, 66] that can be utilized for both classification tasks and regression analysis [67, 68]. CART is a nonparametric ML method. This feature enables the CART method to freely learn any form of the mapping function from the employed training data samples [69]. To detect complicated interdependencies between a series of parameters, CART is capable of using the same parameters more than once in several parts of the model [70]. As a result, this algorithm is flexible and powerful. As the CART method is nonparametric, it does not depend on (or belong to) a specific type of distribution. However, it needs more training datasets, compared to the parametric methods including Naïve Bayes and linear discriminant analysis. It is worth mentioning that outliers in the input parameters do not considerably

affect the CART performance. On the other hand, imbalanced classes may result in under-fitted trees.

This method develops binary trees. Indeed, splitting in CART is performed based on single features. Thus, the CART method is a univariate decision tree. **Fig. 5.1** shows a simple binary tree. It is supposed that $X = (X1, X2)$ is the vector of the independent variables. In the respective order, the values of the threshold and leaf are indicated by T_i and L_i. As can be seen from **Fig. 5.1**, the CART algorithm is a top-down decision tree. The top-down development continues until the stopping criterion (or criteria) is met. For both the regression and classification problems, one of the advantages of the tree-based models is that they can be employed in graphical forms, which do not require calculations. However, it may be not accurate enough for variables that are continuous [71].

There are different splitting criteria for decision trees; namely: impurity-based criteria, information gain, Gini index, likelihood ratio chi-squared statistics, DKM criterion, normalized impurity-based criteria, gain ratio, distance measure, binary criteria, Twoing criterion, orthogonal criterion, Kolmogorov-Smirnov criterion, and AUC splitting criteria. In this work, the Gini index [72] was employed.

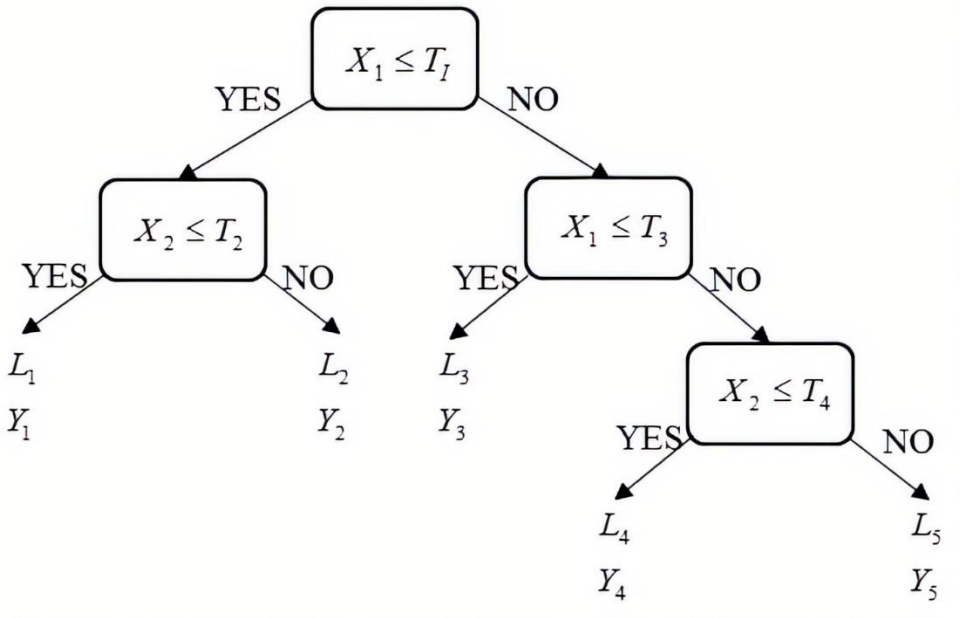


Fig. 5.1: A typical decision tree (adapted from Ref. [78]).

5.4 MODELING PROCEDURE

5.4.1 CAD dataset

To develop a tree-based classifier for CAD diagnosis, the dataset reported by Alizadeh et al. [51], known as the Z-Alizadeh Sani dataset, is employed. The collected databank comprises of the information of 303 patients. This databank has 55 independent parameters and classifies a person into a normal or CAD class. The criterion for classifying a person as a patient who has CAD is her/his diameter narrowing status. If the diameter narrowing is lower than 50%, the patient is classified as normal, and otherwise, as CAD affected [73].

The independent parameters include age, weight, length, gender, body mass index (BMI), diabetes mellitus (DM), hyper tension (HTN), current smoker, ex-smoker, family history (FH), obesity, chronic renal failure (CRF), cerebrovascular accident (CVA), airway disease, thyroid disease, congestive heart failure (CHF), dyslipidemia (DLP), blood pressure (BP), pulse rate (PR), edema, weak peripheral pulse (WPP), lung rates, systolic murmur, diastolic murmur, typical chain pain, dyspnea, function class, atypical, nonanginal CP, low thyroid angina, bundle branch block (BBB), Q wave, ST elevation, ST depression, T inversion, left ventricular hypertrophy (LVH), poor R wave progression, fasting blood sugar (FBS), creatine (Cr), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), blood urea nitrogen (BUN), erythrocyte sedimentation rate (ESR), hemoglobin (HB), potassium (K), exertional CP, sodium (Na), white blood cell (WBC), lymphocyte, neutrophil, platelet (PLT), ejection function (EF), regional wall motion abnormality (region with RWMA), and valvular heart disease (VHD).

Table 5.1 gives the ranges of the independent parameters that have quantifying values. DM, HTN, ex-smoker, smoker, obesity, FH, CVA, CRF, thyroid disease, airway disease, DLP, CHF, edema, weak peripheral pulse, systolic murmur, lung rales, diastolic murmur, typical chest pain, dyspnea, atypical, low threshold angina, exertional CP, nonanginal CP, Q wave, poor R progression, ST depression, ST elevation, T inversion, and LVH are “yes” or “no” parameters. Before introducing

the dataset to the CART algorithm, “yes” and “no” are substituted with one and zero, respectively. Function class is defined by 1, 2, 3 or 4, and region with RWMA is defined by 0, 1, 2, 3 or 4. VHD status is normal (0), mild (1), moderate (2), or severe (3). Finally, female and male are indicated by 0 and 1, respectively.

Table 5.1: Ranges of features of Z-Alizadeh Sani dataset [51].

Parameter	Range
FBS, mg/dl	62-400
TG, mg/dl	37-1050
Cr, mg/dl	0.5-2.2
HDL, mg/dl	15-111
LDL, mg/dl	18-232
BUN, mg/dl	6-52
HB, g/dl	8.9-17.6
ESR, mm/h	1-90
K, mEq/lit	3.0-6.6
Na, mEq/lit	128-156
Lymph, %	7-60
WBC, cells/ml	3700-18000
Neutrophil, %	32-89
EF, %	15-60
PLT, 1000/ml	25-742
BMI, kg/m^2	18-41
PR, ppm	50-110
BP, mmHg	90-190
Weight, kg	48-120
Age, yr	30-86

5.4.3 CART development

In order to develop a CART model for the classification of the Z-Alizadeh Sani dataset into two sub-classes, including CAD and normal, the PyCharm Community Edition 3.1.3 is used. The modeling is performed on a PC with an Intel® Core™ i7-Q740 @ 1.73-2.93 GHz CPU and 8.00 GB RAM. To construct a CART model capable of classifying the patients into normal and CAD, two parameters should be determined/adjusted: the number of features and the maximum depth of the CART.

The number of features is equal to the number of independent parameters in the collected CAD dataset. Hence, there are 55 features. To adjust the maximum depth of the CART (e.g., defined as the maximum length among the existing paths that joins a root of the tree to a leaf), there are no universal rules. In this study, the trial and error procedure is employed to find the optimum maximum depth of the tree. As the starting point, the maximum depth is assumed to be three. Based on the error analysis results, it is found that the CART model offers the best results with an optimum maximum depth of 19. The CART classifier proposed for the diagnosis of CAD is depicted in **Fig. 5.2**.

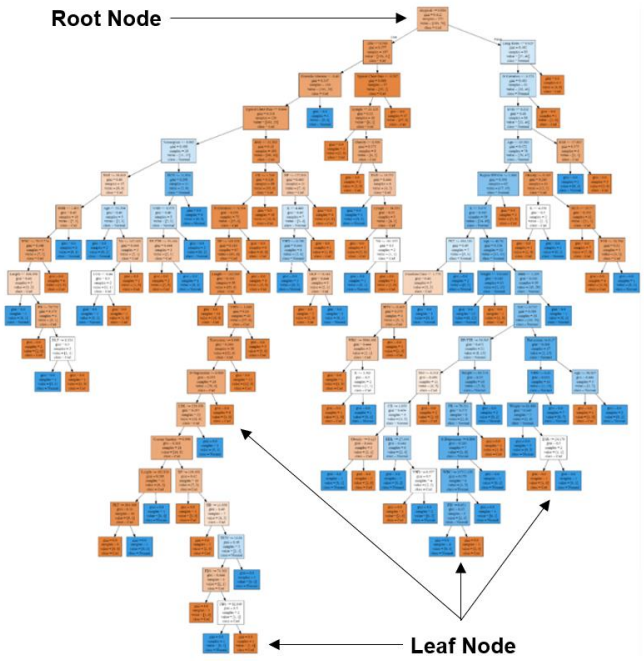


Fig. 5.2: Graphical representation of the CART model (using all features) introduced for CAD diagnosis.

5.4.4 Assessment criteria

This section aims to provide proper criteria for evaluating the performance of the proposed graphical classifier, based on the CART algorithm, in the diagnosis of CAD. The accuracy is one of the main model assessment parameters that defines the proportion of correct classifications. The following expression presents the accuracy in percent (ACC%) [74]:

$$ACC\% = \frac{tn + tp}{tp + fp + fn + tn} \times 100 \qquad (5.3)$$

In Equation (3), *fp*, *fn*, *tn*, and *tp* introduce the false positive, false negative, true negative, and true positive, respectively.

True negative value (TNV) can be defined as the percentage of healthy people that the classification model correctly identifies them as not having CAD. TNV% is defined by Eq. (5.4) as follows [74]:

$$TNV\% = \frac{tn}{tn + fp} \times 100 \qquad (5.4)$$

True positive rate (TPR) measures the proportion of correct CAD predictions to all cases that have CAD. The definition of the TPR (in percent) is given below [74]:

$$TPR\% = \frac{tp}{tp + fn} \times 100 \qquad (5.5)$$

5.5 RESULTS AND DISCUSSIONS

This section includes the main findings/results of this study and corresponding discussions on the relative performance of the input parameters and model performance (compared to the previous approaches). **Table 5.2** shows the contingency table, also known as the confusion matrix, for the Z-Alizadeh Sani databank. According to **Table 5.2**, the accuracy considers the same costs for

misclassified samples. Hence, in addition to the accuracy, TNV and TPR can be employed to perform a comprehensive assessment of the classification models.

Table 5.2: Contingency table of the developed CART models based on the Z-Alizadeh Sani databank.

		CART outcomes	
		Normal	CAD
Targets	Normal	*tn* (correct rejections)	*fp* (Normal is predicted as CAD)
	CAD	*fn* (CAD is predicted as Normal)	*tp* (correct considerations)

It follows that the importance of TPR is higher than TNV, while evaluating the effectiveness of the models developed for the CAD diagnosis. It reveals that correct identification of patients having CAD is more important than identifying healthy people.

The values of the parameters selected as assessment criteria (e.g., ACC%, TNV%, and TPR%) are found to be 100%, concluding that the presented CART model is capable of predicting people having CAD as well as identifying healthy people without any error.

5.5.1 Feature importance

The importance of each feature in the creation of the decision tree-based model (using all the features existing in the Z-Alizah Sani dataset) for CAD diagnosis is graphically demonstrated in **Fig. 5.3**. Based on **Fig. 5.3**, atypical alone has more than 16.5% importance in the development of the CART model when using all the features of the Z-Alizadeh Sani dataset. In addition, some features including neutrophil, poor R wave progression, Q wave, low thyroid angina, dyspnea, systolic murmur, WPP, edema, CHF, thyroid disease, airway disease, CVA, CRF, and EX-smoker have no

impact on the development of the CART model. In other words, the aforesaid features have 0% importance in the tree creation.

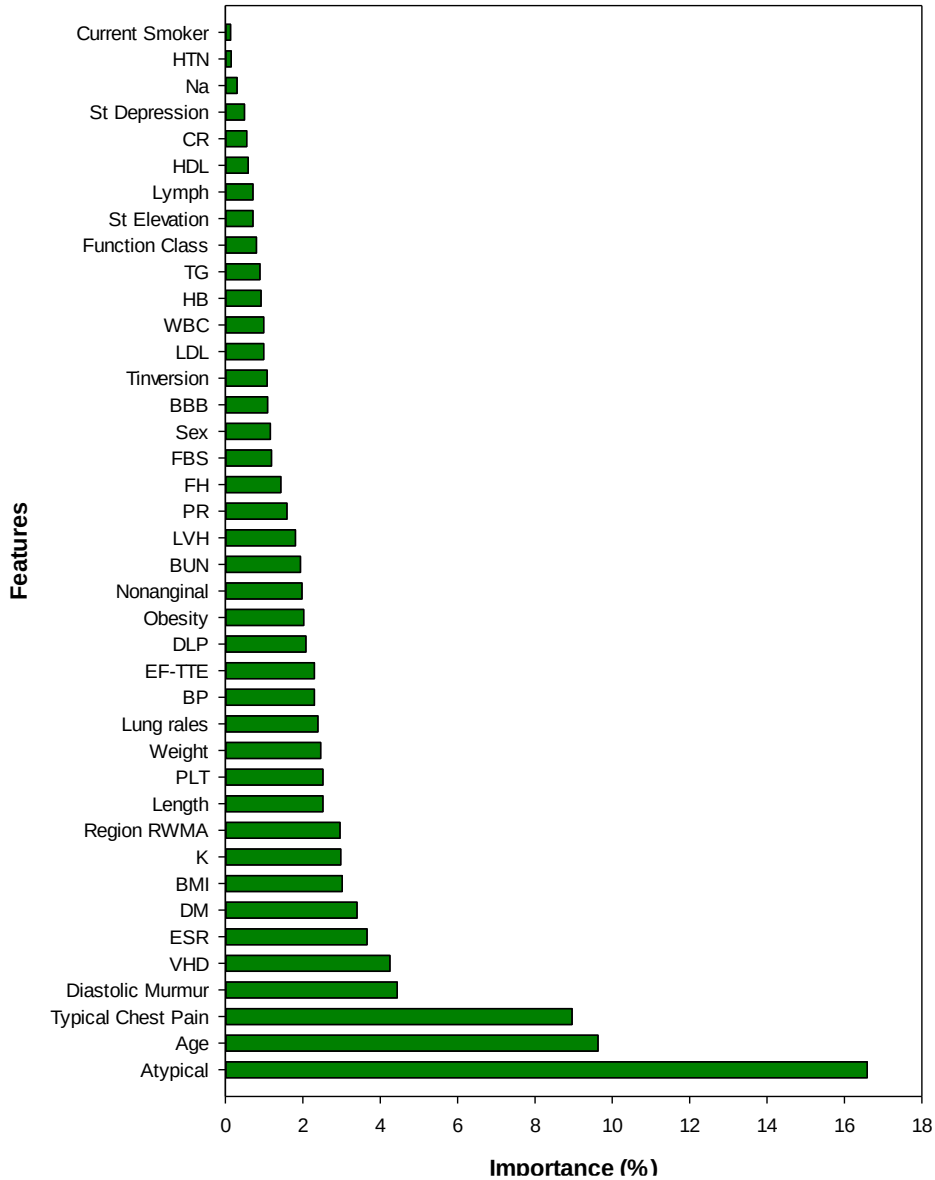


Fig. 5.3: The relative importance of all features involved in the CART model developed for CAD diagnosis/classification.

The independent parameters of the Z-Alizadeh Sani dataset can be categorized into four classes namely symptom and examination, demographic, electrocardiogram (ECG), and laboratory and echo features [51]. **Table 5.3** summarizes the importance of each feature of the aforementioned categories of the dataset for the CART-based CAD diagnosis. According to **Table 5.3**, ECG features, with a 5.18% effect on the creation of the tree, have the lowest importance, compared to other groups. On the other hand, the most important class that influences the structure of the CART classifier is the symptom and examination. The remaining feature classes have approximately equal importance in the predictive model.

Table 5.3: Importance of each feature in the development of the CART model (using all the features) for CAD diagnosis.

Feature Category	Feature Name	Importance (%)
Demographic	Age	9.63
	DM	3.40
	BMI	3.02
	Length	2.52
	Weight	2.46
	DLP	2.08
	Obesity	2.02
	FH	1.43
	Sex	1.16
	HTN	0.15
	Current Smoker	0.13
	EX-Smoker	0.00
	CRF	0.00
	CVA	0.00
	Airway disease	0.00
	Thyroid Disease	0.00
	CHF	0.00
	Total	*28.00*
ECG	LVH	1.81
	BBB	1.09
	T inversion	1.08
	St Elevation	0.71
	St Depression	0.49
	Q Wave	0.00
	Poor R Progression	0.00
	Total	*5.18*

Table 5.3: Continued.

Feature Category	Feature Name	Importance (%)
Laboratory and echo	VHD	4.25
	ESR	3.66
	K	2.98
	Region RWMA	2.96
	PLT	2.52
	EF-TTE	2.30
	BUN	1.94
	FBS	1.19
	LDL	0.99
	WBC	0.99
	HB	0.92
	TG	0.90
	Lymph	0.71
	HDL	0.59
	CR	0.55
	Na	0.30
	Neutrophil	0.00
	Total	*27.75*
Symptom and examination	Atypical	16.60
	Typical Chest Pain	8.96
	Diastolic Murmur	4.44
	Lung rales	2.39
	BP	2.30
	Nonanginal	1.98
	PR	1.60
	Function Class	0.80
	Exertional CP	0.00
	Edema	0.00
	Weak Peripheral Pulse	0.00
	Systolic Murmur	0.00
	Dyspnea	0.00
	Low thyroid angina	0.00
	Total	*39.07*

5.5.2 Reclassification

Based on the importance of the features of the Z-Alizadeh Sani dataset in the development of the CART model (see **Table 5.3)**, this section describes the simple and clear approaches to develop

CART models for CAD diagnosis using selected features. To do so, all features with obtained importance of less than 2% are removed from the dataset, which is logical (and common) in the CART strategy. The remaining features (18 features) are then employed for the creation of a tree-based predictive model. The resulted CART model using 18 selected features classifies the targets with the highest achievable accuracy, TNV, and TPR (100%). The visualized version of the proposed CART model with 18 features is presented in **Fig. 5.4**.

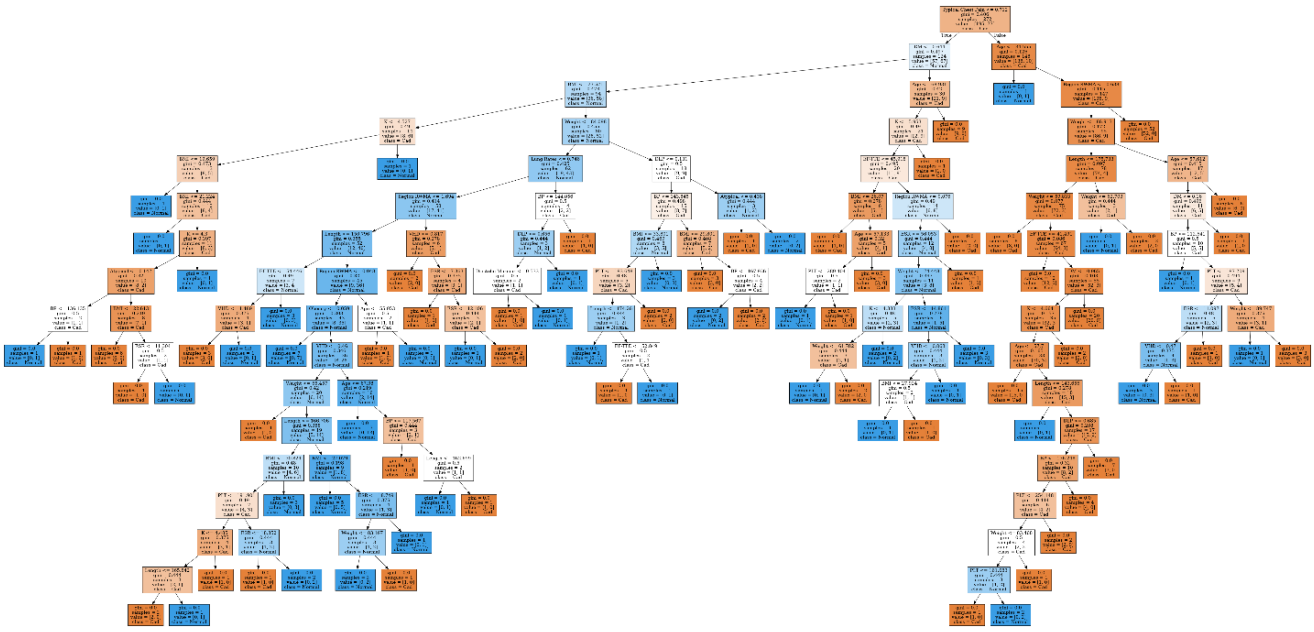


Fig. 5.4: Schematic of a created tree to represent the proposed CART model with 18 features for CAD diagnosis.

To introduce another CART model, the first 10 features that have the highest importance in the developed CART model (referring to **Fig 5.2)** are selected. Similar to the approach used for developing the CART models with all features (see **Fig. 5.2**) and 18 features (see **Fig. 5.4**), the CART classifier with 10 features shows an accuracy, TNV, and TPR of 100%. The created tree-based model with10 selected features is illustrated in **Fig. 5.5**.

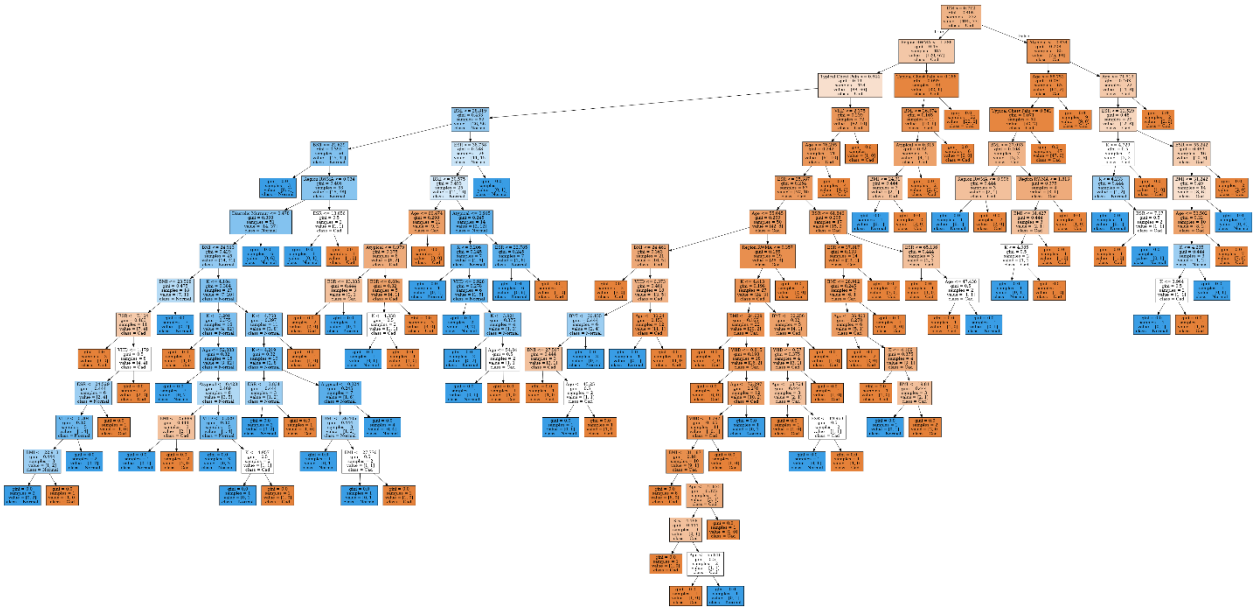


Fig. 5.5: Graphical representation of the developed CART model for diagnosis of CAD while using 10 features.

The importance degree of each selected feature in the development of the CART models using 18 and 10 selected features is listed in **Tables 5.4** and **5.5**, respectively.

Examining the performance of CART methodology in classifying the targets with a limited number of inputs, the next model is developed through including only 5 features namely age, diastolic murmur, typical chest pain, atypical, and VHD. These features are found to be the most influential parameters in the development of the CART model with all the Z-Alizadeh Sani dataset's features. **Fig. 5.6** shows the CART model introduced by 5 selected features. It should be noted that the same dataset splitting procedure is utilized for the development of CART models with 18, 10, and 5 selected features; 90% of the new dataset is dedicated to the training phase, and the remainder of the dataset (10%) is used for model testing.

Table 5.4: Significance of each feature in the development of the CART model (using 18 features) for CAD diagnosis.

Feature Category	Feature Name	Importance (%)
Demographic	Age	8.95
	DM	4.72
	BMI	7.82
	Length	5.49
	Weight	9.25
	DLP	0.78
	Obesity	0.52
	Total	*37.53*
Laboratory and echo	VHD	3.66
	ESR	5.62
	K	3.19
	Region RWMA	5.81
	PLT	4.72
	EF-TTE	3.95
	Total	*26.95*
Symptom and examination	Atypical	1.62
	Typical Chest Pain	27.31
	Diastolic Murmur	0.91
	Lung Rales	0.29
	BP	5.39
	Total	*35.52*

Table 5.5: Importance of each feature in the development of the CART approach with10 features for CAD diagnosis.

Feature Category	Feature Name	Importance (%)
Demographic	Age	11.25
	DM	6.13
	BMI	21.96
	Total	*39.34*
Laboratory and echo	VHD	5.01
	ESR	10.97
	K	8.15
	Region RWMA	9.39
	Total	*33.52*

Table 5.5: Continued.

Feature Category	Feature Name	Importance (%)
Symptom and examination	Atypical	4.64
	Typical Chest Pain	21.57
	Diastolic Murmur	0.93
	Total	*27.14*

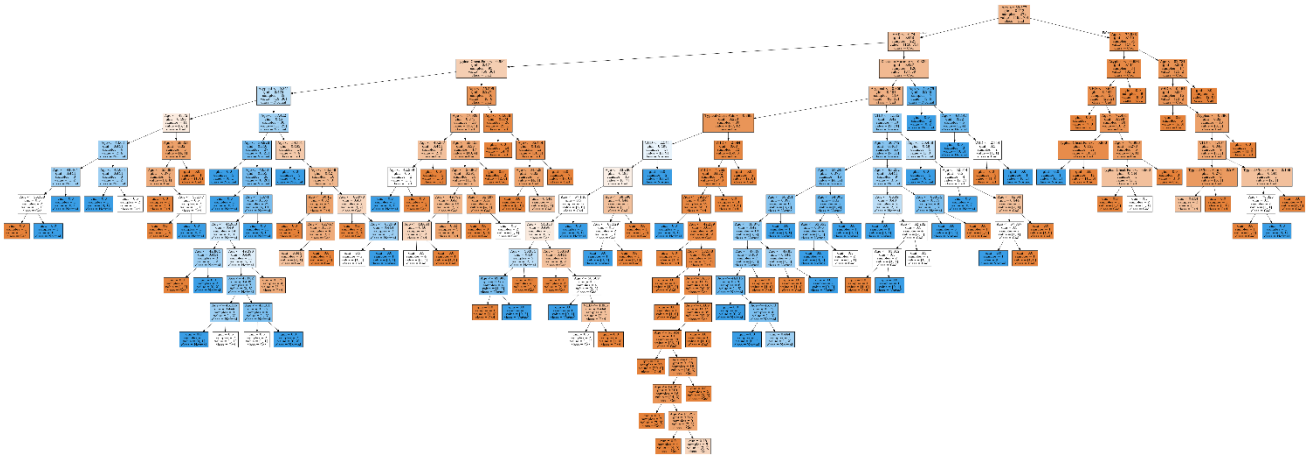


Fig. 5.6: Graphical representation of the CART model with 5 features for CAD diagnosis.

As can be observed from **Fig. 5.2** and **5.4-5.6**, the optimum maximum depths of the trees for the created CARTs with all the features, 18 features, 10 features, and 5 features are 19, 17, 17 and 16, respectively. Hence, it is crucial to employ a comprehensive database for the development of a CART classifier for CAD diagnosis.

Feature importance values for the five-feature CART model are tabulated in **Table 5.6**. According to the results, the age and typical chest pain have the highest significance among all features of the Z-Alizadeh Sani dataset. Indeed, these two CAD risk factors exhibit the most contributions to the development of the tree-based model structure.

Table 5.7 presents the contingency table of the developed CART model with 5 selected features. The contingency table reveals that the highest accuracy cannot be obtained using age, diastolic

murmur, typical chest pain, atypical, and VHD as the independent parameters for the CART methodology, while classifying the Z-Alizadeh Sani dataset.

Table 5.6: Importance of each feature in the development of the CART structure (using 5 features) for CAD diagnosis.

Feature Category	Feature Name	Importance (%)
Demographic	Age	51.72
Laboratory and echo	VHD	3.92
Symptom and examination	Atypical	16.85
	Typical Chest Pain	22.59
	Diastolic Murmur	4.92
	Total	*44.36*

Table 5.7: Contingency table of the developed CART model with 5 features on the basis of the Z-Alizadeh Sani databank.

		CART outcomes	
		Normal	CAD
Targets	Normal	67	20
	CAD	3	213

5.5.3 CART versus literature models

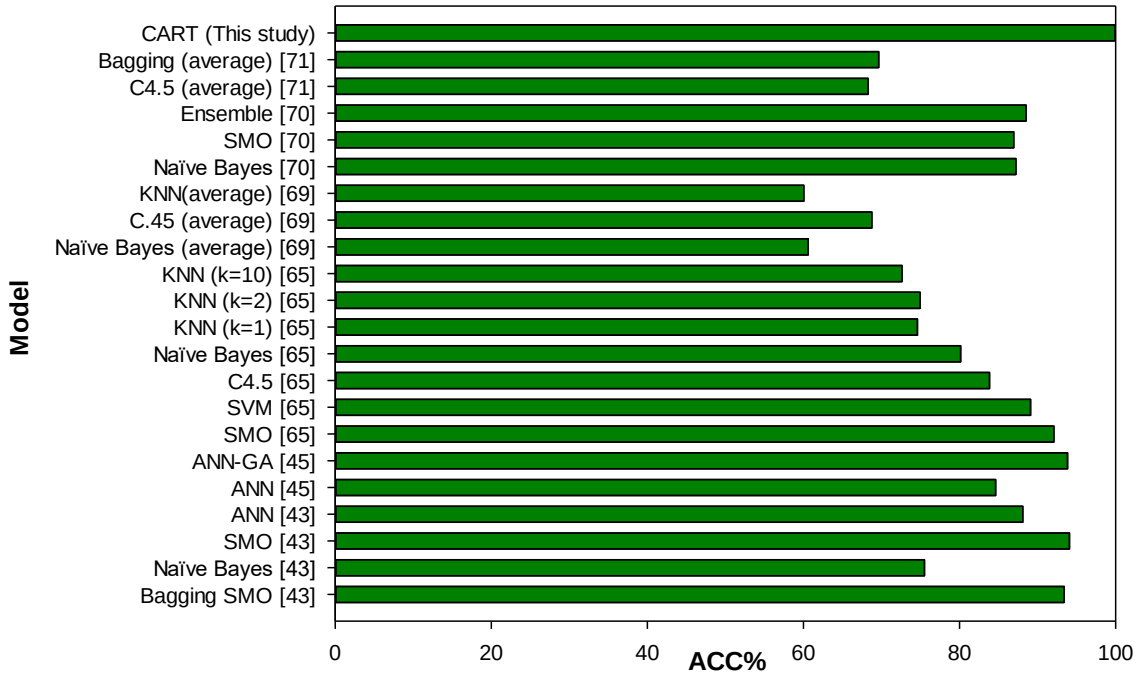
The proposed CART models with all, 18, and 10 features lead to the highest achievable reliability (and accuracy) based on the Z-Alizadeh Sani dataset. The classification performance of the developed CART model with 5 features in the CAD diagnosis is compared to that of the previous models, as seen in **Table 5.8**.

Table 5.8: Error analysis results for the developed CART model (using 5 features) and the literature models while conducting CAD diagnosis.

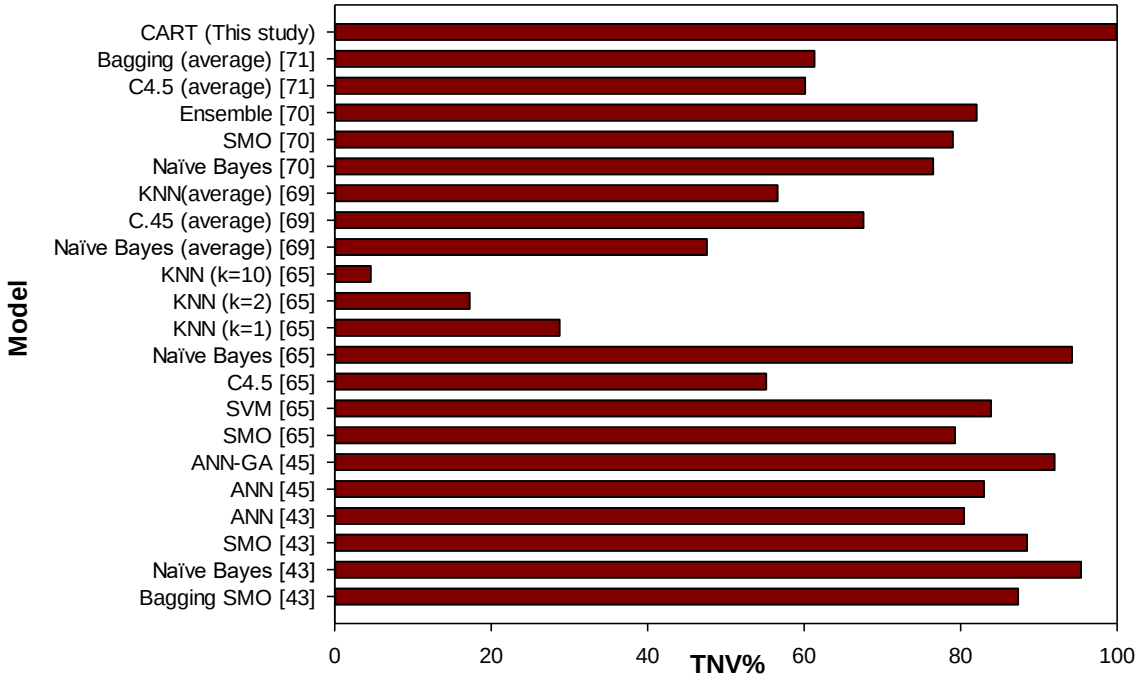
Algorithm	Parameter		
	ACC%	TNV%	TPR%
Bagging SMO [51]	93.40	87.36	95.83
Naïve Bayes [51]	75.51	95.40	67.59
SMO [51]	94.08	88.51	96.30
ANN [51]	88.11	80.46	91.20
ANN [53]	84.62	83.00	86.00
ANN-GA [53]	93.85	92.00	97.00
N2GC-nuSVM [79]	93.08	*	*
SMO [75]	92.09	79.31	97.22
SVM [75]	89.11	83.91	91.20
C4.5 [75]	83.85	55.17	95.37
Naïve Bayes [75]	80.15	94.25	74.54
KNN (k=1) [75]	74.61	28.74	93.06
KNN (k=2) [75]	74.94	17.24	98.15
KNN (k=10) [75]	72.62	4.60	100
Naïve Bayes (average) [76]	60.61	47.56	73.02
C.45 (average) [76]	68.76	67.59	65.80
KNN(average) [76]	60.05	56.62	57.85
Naïve Bayes [80]	87.22	76.50	91.50
SMO [80]	86.95	79.00	90.11
Ensemble [80]	88.52	82.05	91.12
C4.5 (average) [81]	68.30	60.14	71.04
Bagging (average) [81]	69.64	61.32	71.38
J48+MFA (average) [82]	91.09	*	91.10
BF tree+MFA (average) [82]	87.70	*	87.70
REP tree+MFA (average) [82]	84.28	*	84.27
NB tree+MFA (average) [82]	93.77	*	93.77
CART (5 features)	92.41	77.01	98.61

Considering TPR, the KNN (k=10) model [75] gives better results, compared to other approaches **(**see **Table 5.8)**. The NB/SMO model is the best model in terms of TNV extent (accuracy). Although the CART model created with 5 features generates acceptable results, some literature models exhibit greater accuracy and reliability. However, the CART models with all, 18, and 10 features offer 100% accuracy, TNV, and TPR; this accuracy level is not achieved in the previously reported models. **Appendix C** presents the digraphs of all the developed CART models.

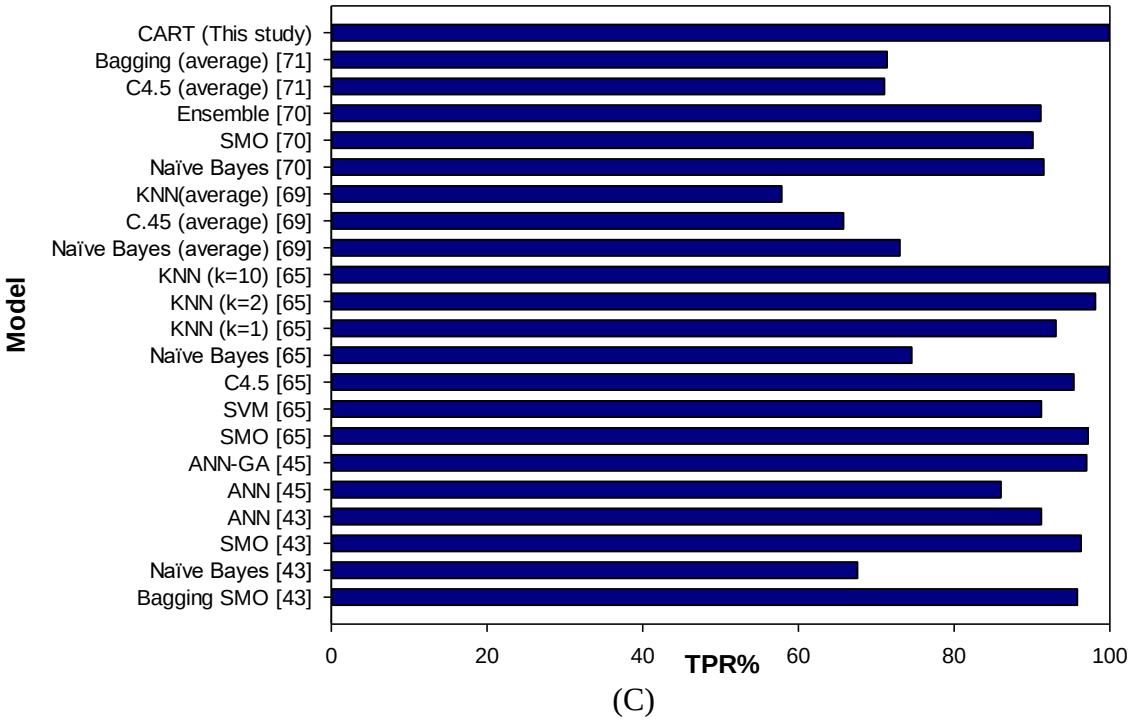
The outcomes of the literature models developed based on algorithms such as Bagging, SMO, Bagging SMO, NB, C4.5, J48, SVM, ANN, and ANN linked with the GA are compared to the predictions of the developed CART models with all, 18 and 10 features in **Fig. 5.7** where the Z-Alizadeh Sani dataset is used.



(A)



(B)



(C)

Fig. 5.7: Comparison of the performance of the developed CART systems with all, 18, and 10 features and the literature models in terms of (A) accuracy, (B) TNV, and (C) TPR.

It is concluded from **Fig. 5.7(A)** that the SMO and Bagging SMO models, presented by Alizadehsani et al. [51], as well as the ANN-GA model, suggested by Arabasadi et al. [53], lead to the highest accurate results, compared to other literature models. Based on **Fig. 5.7(B)** and **5.7(C)**, the values of the TPR% and TNV% for the ANN-GA model [53] are greater than those for the SMO and Bagging SMO models. Therefore, it can be concluded that the ANN-GA [53] is the best literature model. On the other hand, the lowest accuracy and TPR are attained while employing the KNN (average) model, as noticed in **Table 5.8** [76]. It also reveals that the lowest TNV is associated with the KNN model with k=10 [75].

5.5.4 Future work

One of the main advantages of the strategy proposed in this study over other algorithms is that the designed CART-based models can be visualized in an understandable manner. Indeed, there is no need for medical experts to obtain mathematical and computational information regarding the classification methodology. However, comparing the developed CART models with different sets of Z-Alizadeh Sani dataset's features reveals that the structure of the CART classifier is highly sensitive to the employed data points and independent parameters for modeling. The ML approaches are commonly sensitive to the introduced datasets. To obtain satisfactory outcomes, the employed dataset typically needs to be extensive, inclusive, and unbiased. For future studies, it is thus suggested to collect more data from diverse resources for CAD diagnosis/classification. Furthermore, the quality of the datasets for CAD diagnosis can be improved by considering more independent parameters.

According to No Free Lunch Theorem for ML [77], there is no universal model that provides the best results for every problem. Hence, for every analysis, regression or classification, the most common strategy is to implement several ML methods and evaluate their performance and reliability based on statistical parameters. A model developed for a particular objective may be assessed in terms of accuracy and/or complexity. Depending on the nature and importance of the problem, the best model can be selected. As the number and size of datasets for CAD are growing, it is recommended to implement different ML or connectionist tools and find a model that produced the best outcomes for new datasets.

5.6 CONCLUSIONS

Several tree-based classifiers are developed on the basis of the CART algorithm where a recently collected clinical data namely the Z-Alizadeh Sani dataset is utilized for CAD diagnosis. To ensure

that the developed models based on the CART algorithm are reliable, both testing strategies with 10-fold cross validation and with a test sub-dataset are included in the validation process.

Employing ACC%, TPR%, and PPV% as the model assessment criteria, the classification performance of the presented CART models and previous predictive models is evaluated. The findings of the present study reveal that the CART method is capable of classifying individuals as normal or CAD. The CART models developed by considering all, 18, and 10 risk factors of the employed CAD dataset attain the highest precision (and reliability) and no literature model can rival it. The classification results of the CART approach with 5 selected features shows that using only 5 parameters in model development leads to some errors, though the error percentage is still low compared to a majority of the models available in the open sources.

The outcome of this study supports the idea that the CART method is able to present a simple-to-use, reliable, and accurate approach for CAD diagnosis. Hence, the simplicity and robustness of the CART technique when applying to the CAD dataset make this modeling tool as a potential component of a proper healing framework. Furthermore, healthcare professions and postgraduate students can benefit from it. Since the CART classification modeling is highly sensitive to the quality and quantity of the introduced data, a more extensive database for CAD with a greater number of independent parameters might be required for further practical implications of CART tools in hospitals and health centers.

NOMENCLATURES

A_0	Intercept
AACE	American Association of Clinical Endocrinologists
ACC	Accuracy
ACC/AHA	American College of Cardiology/American Heart Association
ANFIS	Adaptive neuro-fuzzy inference system
ANN	Artificial Neural Network
BBB	Bundle branch block

β_i	Regression constants
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CART	Classification and Regression Tree
CHF	Congestive heart failure
Cr	Creatine
CRF	Chronic renal failure
CVA	Cerebrovascular accident
DLP	Dyslipidemia
DM	Diabetes mellitus
EBCT	Electron-beam computed tomography
ECG	Electrocardiogram
EF	Ejection function
ESR	Erythrocyte sedimentation rate
f(x)	The discriminant vector
FBS	Fasting blood sugar
FH	Family history
fn	False negative
fp	False positive
GA	Genetic algorithm
HB	Hemoglobin
HDL	High density lipoprotein
HRV	Heart Rate Variability
HTN	Hyper tension
ID3	Iterative Dichotomiser 3
IT2FLS	Interval type-2 fuzzy logic system
K	Potassium
LDL	Low density lipoprotein
L_i	Value of the leaf
LVH	Left ventricular hypertrophy
ML	Machine learning
MLP	Multi-layer perceptron
Na	Sodium
NB	Naïve Bayes
NMR	Nuclear magnetic resonance
p	Probability of CAD
PCA	Principal component analysis
PLT	Platelet
PR	Pulse rate
RBF	Radial basis function
region with RWMA	Regional wall motion abnormality
RFNN	Recurrent fuzzy neural network
SMO	Sequential Minimal Optimization
SVM	Support Vector Machine

TG	Triglyceride
T_i	Value of the threshold
tn	True negative
TNV	True Negative Value
tp	True positive
TPR	True Positive Rate
USPSTF	US Preventive Services Task Force
VHD	Valvular heart disease
WBC	White blood cell
WHO	World Health Organization
WPP	Weak peripheral pulse
WT	Wavelet transformation
x_i	Risk factors
X	vector of the independent variables
Y	Output of the decision tree

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6 SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

6.1 CHAPTER 2

6.1.1 Summary

Further to the laboratory examinations for BC studies, machine learning and data mining approaches could be implemented for the development of computer-aided BC diagnosis systems. There are several datasets for BC studies. The WBCD is known to be the most employed one for classification modeling using different machine learning and data mining techniques. The primary objective of this review study was identifying published works on the application of smart algorithms for the WBCD classification. To this end, papers published between 1995 and 2020 were reviewed. Moreover, available classification models in the literature were analysed according to some statistical parameters.

6.1.2 Conclusions

As some papers just reported the accuracy of the proposed models, this parameter selected as the main variable for comparisons. This was the major limitation of our study. Based on the error analysis results, it was found that hybrid models are generally effective in classifying the WBCD into malignant or benign cases. Indeed, the majority of the reviewed hybrid methods have flexible capability of nonlinear modeling. Furthermore, it was found that employing feature extraction techniques boosted the overall performance of some classifiers.

However, as some approaches, like ANNs, are known to be black boxes, the resulting model might not be clear and could not be easily understood by non-experts like physicians.

6.1.3 Recommendations

In this study, we just investigated the developed models for the WBCD. As it was mentioned in Chapter 2, there are more datasets like MIAS, IRMA and DDSM. It is recommended that all published papers on the classification modeling using these datasets also be reviewed. Evaluation of the effect of feature extraction techniques on classification performance is also recommended. As mentioned earlier, hybrid models provided excellent outcomes for the WBCD classification. It is recommended to assess the sustainability of different hybrid models on different datasets. Another recommendation is to develop an extensive database with a sufficient number of features for BC investigations. In the case of small datasets like the WBCD, the speed of the employed techniques might not be significant. However, slow performance caused by massive computations is a problem to be solved when big databases are employed. Therefore, researchers are encouraged to evaluate the models in terms of computation speed as well.

6.2 CHAPTER 3

6.2.1 Summary

Classifying the medical datasets using such approaches as ANNs, SVMs and KNNs paves the way to design a more efficient medical diagnostic decision support system. Chapter 3 aimed at employing the RF and ET algorithms to classify the breast cancer type based on the WBCD. To attain the objective, the CART technique was used as a weak learner in conjunction with several RF/ET classification models. It was found that the developed RF models with four to ten CARTs and ET models with three to nine CARTs have high potential to forecast the WBCD type with 100% accuracy in all cases.

6.2.2 Conclusions

The development of classification models for BC diagnosis is of great interest to the researchers. It was revealed that the deterministic models and hybrid approaches existing in the literature offer

acceptable outcomes; however, greater precision in the medicine might considerably affect the diagnosis time, cure/therapy duration, and diagnosis and therapy costs. In addition, a majority of the available tools suffer from higher complexity, lack of optimal structure, and overfitting. The presented RF/ET models are simple to understand and appreciably efficient to categorize the WBCD so that no model can rival this classification strategy in terms of robustness, reliability, implementation speed, and precision.

6.2.3 Recommendations

The presented ensemble models based on the RF and ET methodologies in conjunction with the CART method provided excellent outcomes for the WBCD. However, as machine learning and data mining approaches, like the RF and ET ensemble techniques, are highly sensitive to the employed datasets, it is recommended to evaluate the performance of these approaches for studying other available databases on breast cancer.

Another recommendation would be incorporating optimization algorithms like genetic algorithm and particle swarm optimization algorithm into the investigated ensemble methodologies for future studies. Implementation of hybrid ensemble methods might further simplify and improve the structure of the weak learners of the ensembles.

6.3 CHAPTER 4

6.3.1 Summary

This research employed the CART algorithm to present accurate predictive models capable of analyzing the response of patients having common and/or plantar warts to the cryotherapy and/or immunotherapy methods. To develop a CART classifier for the cryotherapy method, input parameters including the age and gender of patient, number of warts, type of wart, surface area of warts and the time elapsed before treatment are used. In the case of immunotherapy, in addition to

the above-mentioned variables, the induration diameter of the initial test is also considered. To the best of our knowledge, this was the first study on the application of CART-based methods for selection of the best approach for wart removal.

6.3.2 Conclusions

The presented models provide simple-to-employ and accurate tools that can be used by physicians to select the best treatment method for common and/or plantar warts. The performance of the developed classifiers is compared to that of the methods available in the literature in terms of reliability and prediction accuracy. For both cryotherapy and immunotherapy approaches, the outcomes of the proposed CART models offered excellent performance. ACC, TPR, and TNR of the presented models are found to be 100%.

On the other hand, the literature models for the cryotherapy case lead to ACC, TPR, and TNR ranging from 80.0% to 98.9%, 82.0% to 98.9%, and 77.0% to 100%, respectively. For the immunotherapy case, the magnitudes of ACC, TPR, and TNR are between 78.9%-96.7%, 82.2%-97.2%, and 56.7-91.4%, correspondingly. Furthermore, the proposed models appear in a graphical form and can be easily employed in an understandable manner. Hence, it can be concluded that no model can rival the proposed CART models in terms of both accuracy and simplicity of implementation.

6.3.3 Recommendations

The current datasets for the application of interest can be expanded by obtaining further information from various groups of patients. Consequently, we are able to present more efficient (and generalized) decision tree-based models that can be more practical for different cases. Another recommendation is to incorporate capable hybrid and ensemble methodologies (e.g., genetic algorithm and particle swarm optimization) into the CART algorithm for future studies.

Implementation of hybrid/ensemble methods might further simplify (and improve) the structure of the tree-based models developed for wart treatment.

6.4 CHAPTER 5

6.4.1 Summary

Based on the Z-Alizadeh Sani dataset for CAD diagnosis, several classifiers were developed using the CART algorithm. Employing some statistical parameters as the model assessment criteria, the classification performance of the proposed CART models, as well as the literature models, is assessed. The findings of this chapter revealed that the CART algorithm is capable of classifying individuals as normal or CAD. The CART models built by considering all, 18, and 10 risk factors of the used CAD dataset attain the highest precision (and reliability), and no literature model can rival it. The classification results of the CART model with five selected features indicated that using only five parameters in the development process leads to some errors. However, the error percentage is still low compared to a majority of the models available in the open sources.

6.4.2 Conclusions

The outcome of Chapter 5 supports the idea that the CART method is capable of presenting an easy-to-use, reliable and accurate tool for CAD diagnosis. Hence, the simplicity and robustness of the CART technique when applying to the CAD dataset make this modeling tool as a potential component of a proper healing framework. Furthermore, as the CART model is easy to understand, healthcare professions and postgraduate students can benefit from it.

6.4.3 Recommendations

Most machine learning and data mining approaches, including the CART classification algorithm, are highly sensitive to the quality and quantity of the introduced data. Hence, a more extensive

database for CAD with a higher number of independent parameters might be required for further practical implications of CART tools in hospitals and health centers.

APPENDICES

APPENDIX A

Digraphs of the created trees for the RF classification models with 5 to 10 CARTs as well as the ET classification models for breast cancer with 4 to 9 CARTs are provided in an additional file.

APPENDIX B

The digraphs of the CART models proposed in this study for wart treatment are provided as an additional file.

APPENDIX C

This appendix provides digraphs of the CART models created for coronary artery disease.