CAPITAL UNIVERSITY OF SCIENCE AND TECHNOLOGY, ISLAMABAD

Predictive Approach for Tuberculosis Treatment Failure using Patient's Multisource Data of Drug Resistance (TFMDR)

by

Shanza Aqeel

A thesis submitted in partial fulfillment for the degree of Master of Science

in the

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I dedicate this work to my respectful Teachers and my parents who helped me to accomplish this work. Especially to my Parents because without their prayers, moral support and best wishes I couldn't accompalish this work.

CERTIFICATE OF APPROVAL

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(Shanza Aqeel)

Abstract

Tuberculosis (TB) is a very deadly disease caused by a bacterium known as Mycobacterium. More than 10 million were suffering from this disease in 2019 resulting in more than 10% mortalities. The one reason behind mortality is treatment failure due to drug resistance. Predicting treatment outcome beforehand has been proved fruitful for patients because if it is known that the treatment is going to be failed, adaptive measures can be taken such as switching the treatment. The extended research used machine learning models on only demographic and clinical data sources with the highest accuracy of 0.78 on ANN. This study (TFMDR) aims to utilize different machine learning and deep learning models for the prediction of TB treatment outcome. Dataset of seven different countries (Azerbaijan, Belarus, Kazakhstan, Georgia, Moldova, Ukraine and Romania) has been collected from TB Portal. The intuition is that genomic and x-ray features can play a vital role in prediction along with clinical and demographic features, therefore a general feature set comprising of all types of features has been considered for this study. Different feature selection techniques like Information Gain and Ranking have also been utilized to select more relevant features. SMOTE and Class Balancer is used to handle class imbalance problem as failure cases are only 0.10 of whole data. Six experimental setting have been utilized to evaluate proposed approach (TFMDR). The highest performing machine learning model is Random Forest with the accuracy of 0.961 for reduced features set. The highest performing deep learning model is CNN with the highest accuracy of 0.96 for all features set. CNN requires complete set of features which increases the computation of prediction whereas random forest achieved better result with reduced features as compare to CNN.

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Abbreviations

ANN	Artificial Neural Network
AUC	Area under curve
BPKIHS	B.P. Koirala Institute of Health Sciences
CNN	Convolutional Neural Network
DOTS	Directly Observed Treatment, Short-course
KCDC	Korea Centers for Disease Control and Prevention
KNN	K Nearest Neighbout
LASSO	Least Absolute Shrinkage and Selection Operator
MDR-TB	Multi-drug resistance tuberculosis
MTB	Mycobactarium Tuberculosis
NIAID	National Institute for Allergy and Infectious Diseases
OCICB	Office of Cyber Infrastructure and Computational Biology
RR-TB	Rifampicin resistance tuberculosis
SMOTE	Synthetic Minority Oversampling Technique
SVM	Support Vector Machine
TDR-TB	Totally drug resistance tuberculosis
WHO	World Health Organization
XDR-TB	Extensive drug resistance tuberculosis

Chapter 1

Introduction

1.1 Tuberculosis

Tuberculosis (TB) is possibly serious contagious disease that affect the lungs. It can also affect the other organs in the body. It is caused by bacteria called Mycobacterium [1]. TB can be deadly but it is also treatable in many cases [1]. TB is spread from one person to another through air. TB spread in air when person affected with TB, coughs, sneezes or speaks. People can become infected when they breathe nearby these bacteria. TB bacteria can move through blood to other parts of body. It can be in two forms, latent TB (Person doesn't feel sick) and active TB (Person feels sick) [2]. A bad cough that lasts 3 weeks or longer, pain in the chest, coughing up blood or sputum, weakness or fatigue, weight loss, no appetite, chills, fever, sweating at night are the common symptoms of TB [3]. Persons who have been recently infected with TB bacteria, individuals who are drug abusers or have weak immune system are the risk factors of tuberculosis [4].

Tuberculosis (TB) is a very deadly disease caused by a bacterium known as Mycobacterium tuberculosis. More than 10 million were suffering from this disease in 2019 resulting in more than 10% mortalities [5]. The progress of UN in ending the TB disease has also become slow [5, 6]. 1.2 million Children were affected from TB in 2019. It is really difficult to diagnose tuberculosis in children [7]. Eight

countries are highly burdened due to TB in which India is on the top of the list and other countries are Indonesia, China, Pakistan, Nigeria, Bangladesh, South Africa and the Philippines as shown in Figure 1.1 [8].

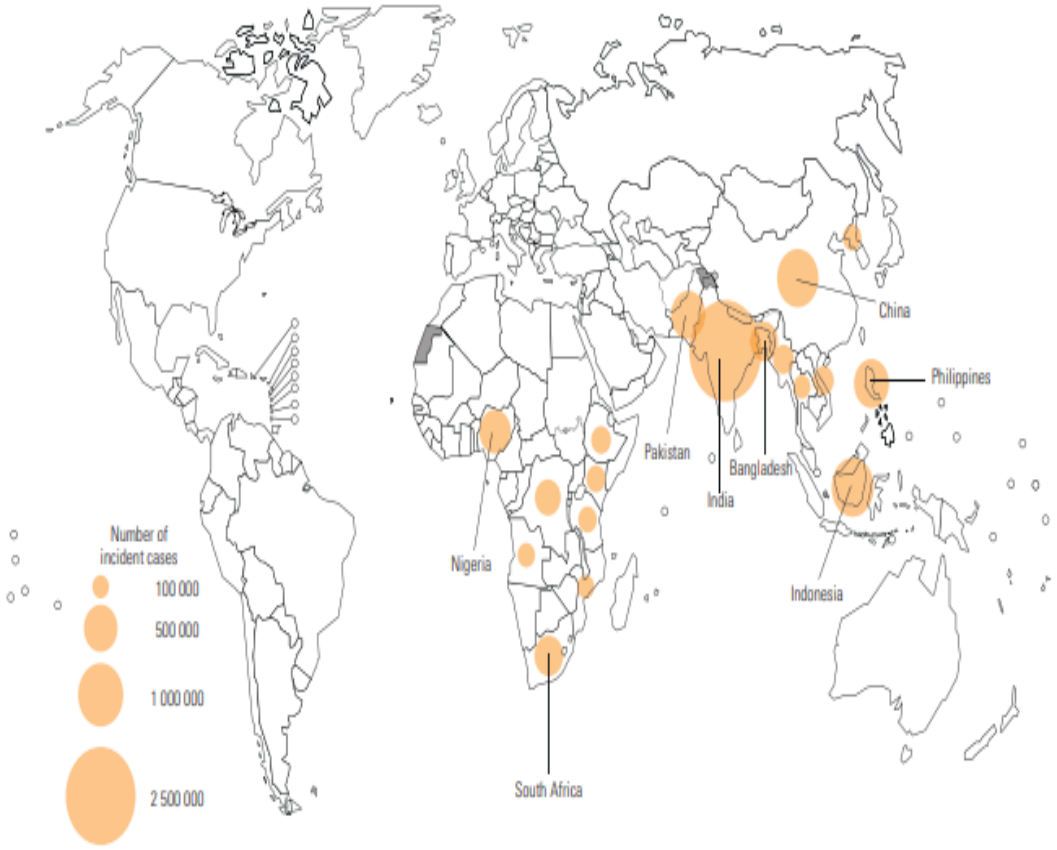


FIGURE 1.1: Tuberculosis cases of top eight countries in 2019[8]

In 2019, 87% cases of TB were encountered [7]. Tuberculosis diagnosis and treatment was helpful to save 60 million people from tuberculosis between 2000 to 2019 [7]. Many patients of tuberculosis also diagnosed with HIV as HIV weakens the immune system and increases the risk of tuberculosis. 1.2 million People died because of this deadliest disease which were HIV-negative but 208, 000 people died because of TB as well as HIV. Total 88% of adults were accounted for tuberculosis out of which 12% children who were 15 years or less, died because of this deadliest disease [5].

1.2 Types of Tuberculosis

Tuberculosis is neo-latin word where 'tubercle' means round nodule/swelling and 'osis' means condition. There are two main types of tuberculosis which are pulmonary (related to lungs) and extrapulmonary (related to parts other than lungs). These two types are further classified into several other types. Types of tuberculosis are given in Figure 1.2.

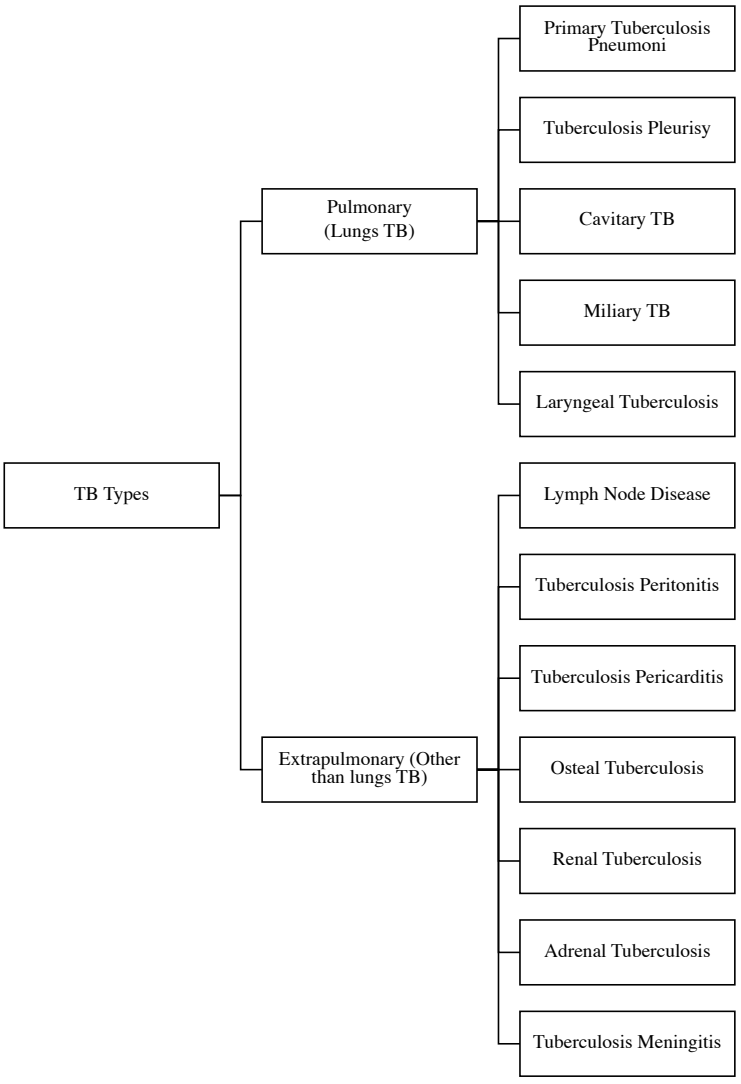


FIGURE 1.2: Tuberculosis types [9–11].

1.2.1 Pulmonary TB

Type of TB which is related to lungs is called pulmonary TB. Infection of the lungs is main cause of this TB. It's extremely infectious because it can transmit through droplets. 50% patients of pulmonary tuberculosis would die if they are not treated properly [12].

Symptoms of pulmonary Tuberculosis are as follows:
Central: fatigue, loss of appetite
Lungs: productive cough , coughing up blood, chest pain
Skin: night sweats

Pulmonary tuberculosis is further divided into these categories:

- **Primary Tuberculosis Pneumonia**

This infectious disease is a respiratory disease. High fever and productive cough are the most common symptoms of this type of TB. It's mostly happens and youngsters and in adults also. It's also found in patients that have immunological disorder e.g., HIV/AIDS patients etc.

- **Tuberculosis Pleurisy**

It occurs in the space between lung and bronchi and describe as pleuritis secondary. Common symptoms are chest pain and productive cough. Some other symptoms are night sweats, fever, malaise, weight loss. It mostly occurs in patients who are immunocompetent such as youngsters.

- **Cavitary TB**

The higher lobes of the respiratory organ contain cavitary drain. By forming cavities or expanding air zones the bacterium causes gradual destruction of the respiratory system. In reactivation disease, this type of TB occurs. The largely

oxygenated (a environment within which M. TB grows) higher lobs of the respiratory organs are affected. Rarely, after primary infection, the cavitary TB is present. Productive coughing, night sweat, fever, loss of weight and weakness are present.

- **Miliary TB**

Miliary tuberculosis is an active TB that affects liver, bone marrow and lungs. It can also affect other body parts like brain, spinal cord and heart. Common symptoms of miliary tuberculosis are chills, fever, weakness, difficulty breathing, general discomfort and weight loss. If it is related to bone marrow it can cause anemia or blood abnormalities.

- **Laryngeal Tuberculosis**

It is very infectious. This type of pulmonary TB can infect the vocal cord area or the larynx.

1.2.2 Extrapulmonary TB

Extrapulmonary TB (Tuberculosis) that are not related to the lungs but parts other than lungs is known as extra-pulmonary. Almost 15-20% of all the TB (Tuberculosis) are extrapulmonary. It mostly occurs in young children and persons with weak immunity [12].

Extrapulmonary TB further divides into:

- **Lymph Node Disease**

The uncontrolled replication of bacteria is contained in any lymph gland, causing the lymph gland to enlarge. A fistula from the lymph gland to the skin is developed. The infection is a natural consequence.

- **Tuberculosis Peritonitis**

It affects the peritoneum (membrane that connects internal organs in abdomen). It is caused by the gastrointestinal tract tuberculosis. It can be in dry, wet and fibrotic forms.

- **Tuberculosis Pericarditis**

In this type of extra-pulmonary tuberculosis, the membrane near the heart (pericardium) is affected. This leads to fluid fills in the area between the serosa and the heart, which obstructs the heart's blood filling and effectiveness.

- **Osteal Tuberculosis**

It is related to joint, bones or both structures. Any bone can become infected, but the spine is one of the most common places. Spinal infection can lead to compression and rear abnormality.

- **Renal Tuberculosis**

This form of extrapulmonary tuberculosis affects the kidneys.Mostly medulla (inner part of kidney) is affected. Infection can spread in kidneys through blood. People having other diseases like HIV and diabaties etc are the risk factors of renal Tuberculosis.

- **Adrenal Tuberculosis**

Adrenal tuberculosis will cause insufficient adrenal disease. This disorder result in too low or too high production of hormones. Adrian failure in the steroid in times of stress, weakness and collapse is the inability to increase steroid production.

- **Tuberculosis Meningitis (Brain Tuberculosis)**

The main membrane near the brain and the backbone is infected by TB meningitis. This could be catastrophic, leading to chronic disability and death. TB is often troubling to discern from a tumor in the brain because it should have focal neurological signs within the brain.

1.3 Tuberculosis in Pakistan

In 2018, an estimated 562,000 people in Pakistan were diagnosed with tuberculosis. This is the approximate number of HIV-negative people. In addition, about 3,800 people living with HIV are infected with tuberculosis. In terms of population, Pakistan is the 6th most populous country in the world. Maximum TB load. Pakistan has an likely 27,000 cases of drug-resistant tuberculosis each year. Among the 30 countries with a high incidence of tuberculosis, Pakistan also ranks sixth in drug-resistance tuberculosis. This means that there is a vast gap of approximately 200,000 people among the number of people reported and the estimated number of untreated tuberculosis patient [13].

Of the 369,548 cases notified:

1. At the time of diagnosis 22% cases were tested with rapid diagnostics
2. 20% cases with HIV status
3. 80% were pulmonary TB cases
4. 48% were bacteriological confirmed cases
5. 13% children's cases of age 0-14 years
6. 42% women
7. 45% men

Almost 44,000 with HIV negative, die from tuberculosis every year and 1300 patient with HIV positive also die.

Key reasons are:

1. Delays in diagnosis
2. Treatment of the affected patient
3. Deficient drug regimens
4. Poor follow up, no dosage record keeping

Table 1.1 shows the TB treatment cases reported in 3rd quarter of 2020. The table shows the data of Punjab, Sindh, KP, Balochistan, F.A.T.A, Gilgit Baltistan, AJK and ICT.

TABLE 1.1: Provincial and territorial TB statistics Pakistan [14]

TUBERCULOSIS REPORT
Period: 3rd Quarter, 2020

Provinces/Regions	TB Cases B+ (N + R)	Case Detection Rate B+	TB All Types			CDR Total	% Treatment Success Rate* (TSR)
			Male	Female	Total		
Punjab	41145	60%	21213	19932	41145	53%	NA
Sindh	16341	61%	8784	7557	16341	48%	NA
KP	10137	36%	5340	4797	10137	46%	NA
Balochistan	2451	31%	1153	1298	2451	27%	NA
F. A. T. A	1084	23%	544	540	1084	31%	NA
Gilgit Baltistan	690	17%	369	321	690	66%	NA
AJK	1079	47%	592	487	1079	38%	NA
ICT	232	19%	134	98	232	15%	NA
Pakistan	73159	53%	28129	35030	73159	48%	NA

B+:BacteriologicallyPositive N+:NewCase R:RelapseCases

National Tuberculosis Program (NTP)

NTP was established in 1995 with a mission to monitor tuberculosis nationwide through the DOTS strategy and quality treatment from public health services and other stakeholders, including the private sector and non-governmental organizations. The NTP is responsible for maintaining the national tuberculosis control plan [15].

Key Performance Indicators

1. Every 100,000 TB cases (all forms) reported by NTP are in Pakistan each year [16].
2. The percentage of successfully treated tuberculosis cases among the bacteriologically confirmed cases reported by NTP in Pakistan [16].
3. The number of suspected MDR-TB cases reported and treated [16].

1.4 Tuberculosis Treatment

Treatment therapy of tuberculosis depends upon the type and level (active and latent) of tuberculosis. In latent TB person doesn't feel sick and symptoms are not clear. In active TB symptoms are clear and person feels sick. Different types of drugs are used as per severity of disease.

- **First Line Drugs**

First-line anti-TB drugs are mainly used for medical conditions, drugs with high clinical efficacy and minimal side effects are mostly selected. Isoniazed and Rifampicin are the most commonly used first line drugs.

- **Second Line Drugs**

Used when first-line anti TB drugs have no influence on the disease and patients are difficult to treat due to side effects. These drugs are used in pairs. Either second line drugs are used with fluoroquinolones or injectable drugs are used.

Figure 1.3 shows drugs used for tuberculosis treatment.

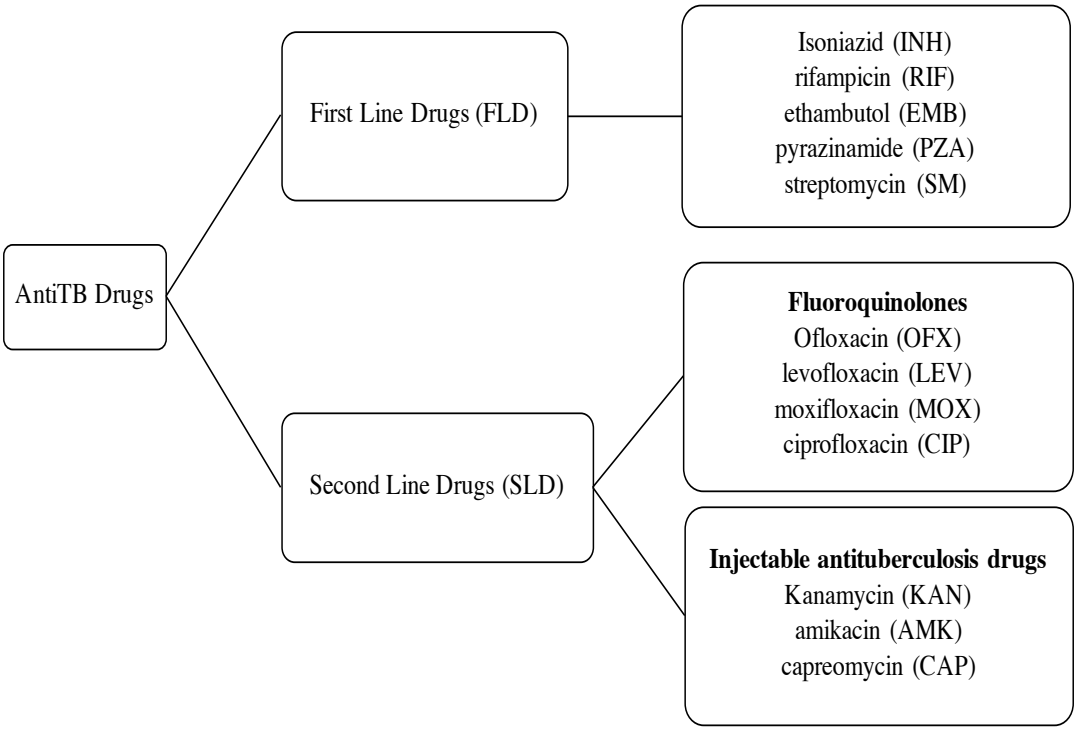


FIGURE 1.3: Drugs for tuberculosis treatment [11, 17, 18].

1.4.1 Tuberculosis Treatment Outcomes

Tuberculosis treatment results in seven outcomes. Tuberculosis treatment outcomes are shown in Table 1.2

TABLE 1.2: TB treatment outcome definitions

Outcome	Definition
Cured	When therapy is successful then patient fell in this category.
Completed	When the patient completes the duration of therapy.
Lost to Followup	When the patient reallocates.
Relapse	When patient is diagnosed again after the treatment.
Failure	When patient is not treated properly or do not take medication.

Died	-
Default	Intervention in treatment for 22 months or more

1.5 Challenging Areas of Tuberculosis Treatment

There are certain challenges relevant to the TB disease which addressed based on certain classification:

- Development of reliable way to diagnose TB[19–21]
- Prediction of TB treatment that either it will fail or not so that doctors can adjust the treatment/ medicine accordingly [19–21]
- Prevention of TB [19]
- Anti-tuberculous drugs development [22, 23]
- Development of new methods for testing drug sensitivity [20, 22]
- Understanding phenotypic and genetic markers of TB resistance[20, 22]
- Prediction of treatment duration by developing an animal model [22]
- Identifying social risk factor role in communities to control infection [22]

One of the major obstacles of TB control is the accurate detection and diagnosis. Diagnosis required a toolbox which is not sufficient. Diagnostic delay often results in serious consequences. Studies [19–21] focused on TB diagnosis so that it can be improved.

Tb prevention can reduce the risk of TB progression by 90%. Avoiding Tb prevention therapy can cause TB infection to become active TB. Study [19] explains the methods for better TB prevention.

Drug-resistant tuberculosis is difficult to treat as it is a long and complex process. Because of MDR-TB, XDR-TB and TDR-TB, it is difficult to control tuberculosis. various methods have been introduced to treat drug resistance tuberculosis. Many drugs have been introduced which are effective against resistance strains. Studies [20, 22] discussed the development of drugs for treatment of tuberculosis.

However, our focus is on the prediction of TB treatment failure because due to mismanagement many patients lead to death. TB treatment failure is not easy to predict because of the complexity of these features, their association among certain criteria's and the extraction of these features from multiple sources. It is difficult to identify feature which will cause the TB treatment failure [24–26].

1.6 Importance of TB Treatment Failure

Tuberculosis treatment failure, defined as a positive smear microscopy or sputum culture test five months or more after the start of anti-tuberculosis treatment. Patients who fail the treatment have higher morbidity (long lasting medical condition) and mortality(death rate) than cured patients. Percentage of TB treatment failure cases from 2009 to 2018 are given in Figure 1.4.

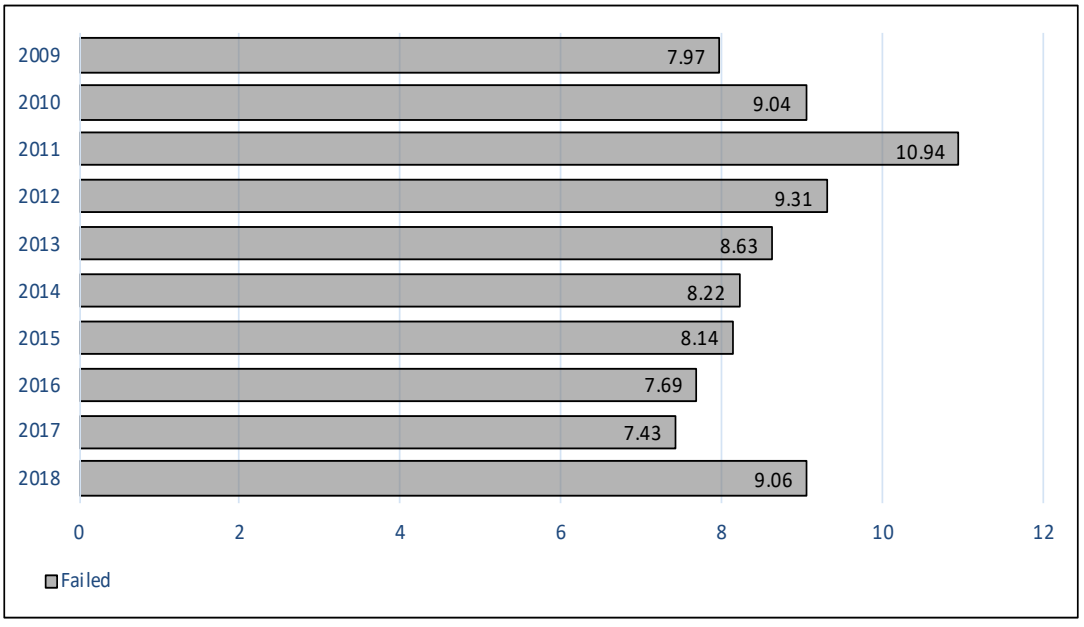


FIGURE 1.4: Percentage of TB treatment failure cases [27].

1.6.1 Reasons of TB Treatment Failure

There are many reasons of treatment failure worldwide. One of the main reasons of treatment failure is irregularity in medication. It is curable by certain types of drugs known as first line drugs, however bacterium evolves with the time being by mismanagement of treatment resulting in a very severe form of TB which are resistant to drugs for simple TB [6]. These severe forms of TB are called multi-drug resistant and extensive drug resistant. This form of TB is also the cause of TB treatment failure. Low case detection, no surveillance of transferred TB patents, lost to follow up, these are also some reasons of TB treatment failure. Cases of treatment failures are increasing in the world. It is very important to find the actual reasons of treatment failure so that patients can be treated properly and ratio of treatment failure could be reduced.

One of the main reasons of TB treatment failure is drug resistance. The relationship between treatment duration and drug resistance may reflect the prolonged treatment time of drug-resistant patients due to treatment failure; it may also reflect irregular previous tuberculosis treatments that led to drug resistance.

1.6.2 Drug Resistance Tuberculosis

Drug resistance tuberculosis is the main reason of TB treatment failure. There are many types of drug resistance tuberculosis but MDR and XDR are very common.

MDR The mishandling/mismanaging of TB treatment leads to a severe kind of TB known as MDR which is resistant to at least isoniazid (INH) and rifampicin (RIF) and second-line drugs are used in this case [4].

XDR The mishandling/mismanaging of MDR-TB treatment leads to more severe kind of TB known as XDR that is resistant to either rifampicin or isoniazid like MDR tuberculosis, any fluoroquinolone, and at least one of three second-line injectable anti-tuberculosis drugs. It is very difficult to treat. [28].

First-line drugs, which are commonly used for treating tuberculosis such as rifampicin, isoniazid, pyrazinamide and ethambutol, are becoming ineffective due to mutations in certain genes. These genetic markers are essential for the identification and classification of drug-resistant strains and most importantly give scientists an opportunity to design drugs, which counteract the effects of these mutations. MDR-TB shows resistance to at least one of the two most drugs: isoniazid (INH) and rifampicin (RIF) [28, 29].

The emergence of XDR-TB resistance is due to having developed resistance to both rifampicin and isoniazid, as well as to fluoroquinolones and at least one of the second-line drugs (i.e., kanamycin, capreomycin, or amikacin) [29]. Infections with XDR strains are essentially incurable by the currently available TB drugs. Therefore, these resistant strains of mycobacterium tuberculosis pose a serious threat to global control of TB.

Figure 1.5 shows the different type of drug resistance tuberculosis and drugs which they resist.

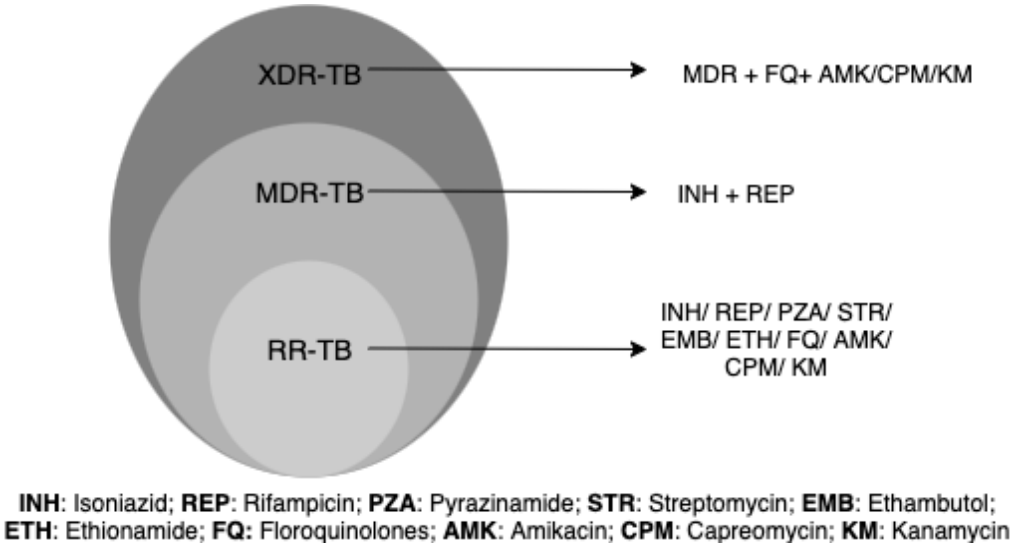


FIGURE 1.5: Types of drug resistance TB with resistant to specific anti-TB drugs [29].

The existence of genetic markers makes the possibility of drug resistance very high, and it will be very helpful as a diagnostic tool. Determining resistance of drug in tuberculosis involves finding a list of genes known to be associated

with resistance to specific drugs. Recently, some molecular approaches have been recommended for the detection of drug resistance in a shorter time frame and rapid detection of markers of multi-drug resistance. The current generation of NGS analysis helps to detect mutations and is considered significant for understanding its effects. Advances in sequencing technology have achieved complete sequencing of the mycobacterial genome and provided complete mutation analysis information to identify drug resistance patterns. And a faster alternative to resistance testing.

Other types of Drug Resistance Tuberculosis are shown in Table 1.3

TABLE 1.3: Types of drug resistance tuberculosis.

Type	**Defination**
Mono Resistance	It resists to any one anti-Tb drug
Poly Resistance	Including rifampicin and isoniazid, it resists to one or more anti-TB drug
Multi Drug Resistance (MDR)	Resists both rifampicin and isoniazid
Extensive Drug Resistance (XDR)	If there is resistance to any three injectable second line drug i.e amikacin, kanamycin and capreomycin or to any fluoroquinolone or any MDR.
Rifampicin Resistance (RR)	Any resistance to rifampicin is called RR. It can be poly-resistance, mono resistance, MDR or XDR.

There are two ways that people get Drug Resistance Tuberculosis.

- First, if not treated properly, people will develop drug-resistant tuberculosis. There may be many reasons for this, including the patient's failure to follow

an appropriate TB treatment regimen. It may also be that the wrong anti-tuberculosis drug was prescribed. Or use inferior anti-tuberculosis drugs [30].

- Second, infectious or primary drug-resistant tuberculosis is the result of direct transmission of drug-resistant tuberculosis from one person to another [30].

1.7 Existing Studies of Tuberculosis Treatment

Many machine learning models have been used to extract the feature that can cause TB treatment failure. Forward step-wise selection, backward selection, Random Forest, SVM are the main machine learning models used in TB treatment failure prediction [24, 31, 32]. Deep learning technology use pipeline architecture in which different graphical features could also be extracted. Some studies used Deep learning model to predict drug resistance in TB patient [6, 33].

As MDR/XDR is one of the main origins of TB treatment failure. The study [34] focuses on the factors that cause a treatment to fail and how MDR/XDR is developed. Recently most studies predict the drug resistance using whole-genome sequencing [35]. The work existing in [24, 25]focuses on the treatment failure prediction using machine learning algorithms. The main objective is to find the patients which are at higher risk and explore the factors that can lead to treatment failure.

TB has high mortality rate because of delayed and mismanagement of treatment. There is a need of early prediction if a person would have any type of TB along the symptoms of treatment failure as well. The health care provider (doctors) can prescribe his/her treatment plans in TB treatment by keeping in mind failure type. This might improve the percentage of TB treatment failure on later stages by following the prescribed as per system prediction. TB treatment failure is not easy to predict because of the complexity of these features, their association among

certain criteria's and the extraction of these features from multiple sources. However, Deep learning might provide more promising results by extracting different features from the dataset and considering different diseases affecting it like HIV. The focus of this research is to discover the generalized set of features to predict treatment failure of tuberculosis using deep learning methods. If this can be done then treatment of the tuberculosis patient can be done in better way.

Our objective is to implement a machine learning and deep learning model using wide range of features for prediction of TB treatment failure which is a very complex task. The scope of our research is very wide and require a lot of time. We might use different models for better results. Our dataset is very large and complex and a lot of features will be used from it. We also want to predict multiclass outcome which further increases the complexity of task.

1.8 Tuberculosis Treatment Features

Mainly there are multiple sources to extract the data which include clinical, demographic, genomic and the data of X-rays. Because of the multiple sources generating multiple features it is complex to identify feature which can cause TB treatment failure. Table 1.4 shows the features used in this research.

Table 1.4: TB treatment features

No	**Feature Name**	**No**	**Feature Name**
1	age of onset	2	gender
3	country	4	education
5	employment	6	number of children
7	number of daily contacts	8	case definition
9	type of resistance	10	bmi
11	lung localization	12	xray count
13	organization	14	image body site
15	dissemination	16	lungcavity size

17	anomaly of mediastinum vessels develop	18	affect_pleura
19	shadow pattern	20	$\text{affect}_{l}evel$
21	pneumothorax	22	plevritis
23	affected segments	24	nodicalcinatum
25	process prevalence	26	thromboembolism of the pulmonaryartery
27	posttbresiduals	28	$\text{lung}_{c}apacity_{d}ecrease$
29	bronchial obstruction	30	anomaly of lungdevelop
31	accumulation of contrast	32	limfoadenopatia
33	totalcavernum	34	overall percent of abnormal volume
35	pleural effusion percent of hemithorax involved	36	ispleuraleffusionbilateral
37	other non tb abnormalities	38	are mediastinal lymphnodes present
39	rater	40	collapse
41	smallcavities	42	mediumcavities
43	largecavities	44	is any large cavity be long to a multisextant cavity
45	can multiple cavities be seen	46	infiltrate lowgroundglassdensity
47	infiltrate mediumdensity	48	infiltrate highdensity
49	smallnodules	50	mediumnodules
51	largenodules	52	hugenodules
53	is any calcified orpartially calcified nodule exist	54	is any non calcified nodule exist
55	is any clustered nodule exists	56	are multiple nodule exists
57	low ground glass density active fresh nodules	58	medium density stabalized fibrotic nodules
59	high density calcified typically sequella	60	culture

61	culturetype	62	microscopy
63	bactec test	64	le test
65	hain test	66	lpaother test
67	genexpert test	68	bactec isoniazid
69	bactec rifampicin	70	bactec streptomycin
71	bactec ethambutol	72	bactec ofloxacin
73	bactec capreomycin	74	bactec amikacin
75	bactec kanamycin	76	bactec pyrazinamide
77	bactec levofloxacin	78	bactec moxifloxacin
79	bactec p aminosalicylic acid	80	bactec prothionamide
81	bactec cycloserine	82	bactec delamanid
83	bactec bedaquiline	84	bactec linezolid
85	bactec clofazimine	86	bactec aminoglycosides injectible agents
87	le isoniazid	88	le rifampicin
89	le streptomycin	90	le ethambutol
91	le ofloxacin	92	le capreomycin
93	le amikacin	94	le kanamycin
95	le pyrazinamide	96	le levofloxacin
97	le moxifloxacin	98	le p aminosalicylic acid
99	le prothionamide	100	le cycloserine
101	hain isoniazid	102	hain rifampicin
103	hain ethambutol	104	hain ofloxacin
105	hain capreomycin	106	hain amikacin
107	hain kanamycin	108	hain levofloxacin
109	hain moxifloxacin	110	hain prothionamide
111	hain fluoroquinolones	112	hain aminogly cosides injectible agents
113	lpaother ofloxacin	114	lpaother capreomycin
115	lpaother amikacin	116	lpaother kanamycin
117	lpaother levofloxacin	118	lpaother moxifloxacin

119	lpaother fluoroquinolones	120	lpaother aminogly cosides injectible agents
121	genexpert rifampicin	122	period start
123	period end	124	period span
125	regimen count	126	qure hilarlymph adenopathy
127	treatment status	128	regimen drug
129	stemcell dose	130	social risk factors
131	comorbidity	132	specimen
133	lineage	134	ncbi sourceorganism
135	ncbi bioproject	136	gene name
137	high confidence	138	hain
139	genexpert	140	xray exists
141	ct exists	142	qure bluntedcp
143	qure abnormal	144	qure consolidation
145	qure fibrosis	146	qure opacity
147	qure peffusion	148	qure tuberculosis
149	qure nodule	150	qure cavity

Summary

This chapter discusses about the Tuberculosis. What is tuberculosis and how the world is affected by this disease? What are the types of tuberculosis and how it spread? Treatment outcomes and different drugs to treat the tuberculosis are also discussed. What are the reason for the TB treatment failure. Drug resistance which is one reason for tuberculosis treatment failure and different types of drug resistance TB are also discussed. This chapter also contain the features used in TB treatment failure. In chapter 2 literature review will be explained.

Chapter 2

Literature Review

2.1 Introduction

In tuberculosis domain, various studies focused focused on tuberculosis diagnosis, treatment failure, prevention of tuberculosis, anti-TB drugs development, testing drug sensitivity and identification of risk factors. This research focuses on TB treatment failure prediction. Literature has been categorized into three sections based on previous researches. There are studies which involve on identifying the features which can cause TB treatment failure [26, 36–40]. Other studies apply different sources of features to predict treatment failure using machine learning Models [24, 25, 31, 32, 41, 42]. Due to diversity and complexity of features some studies used Deep Learning model for the prediction of Tuberculosis and its treatment [6, 33, 43–45].

Section 2.2 of this chapter discusses the feature identification approaches. Section 2.3 explains the studies which uses machine learning models for the prediction of TB treatment failure. Section 2.4 discusses the studies which uses deep learning models in tuberculosis domain.

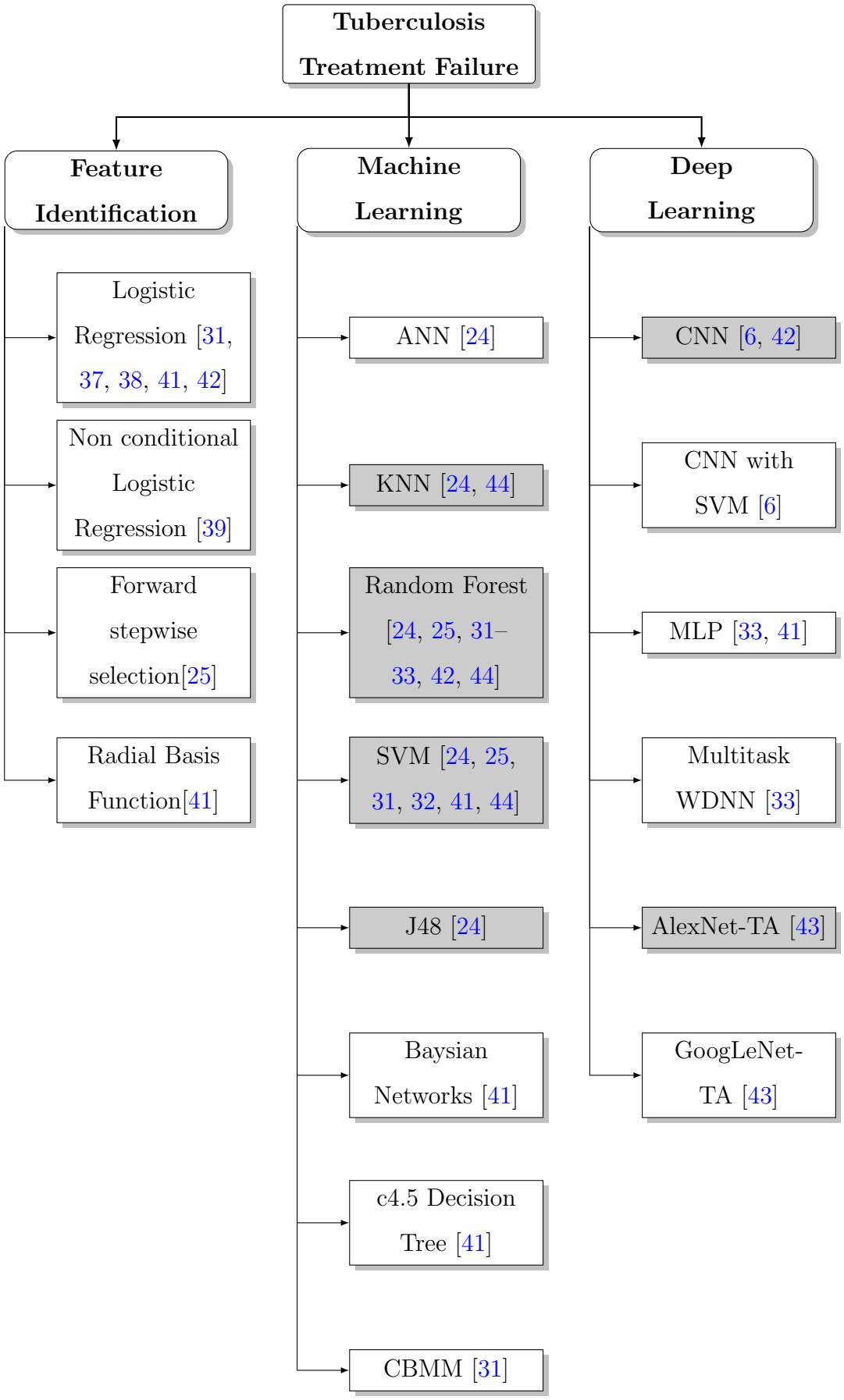


FIGURE 2.1: Approaches used in tuberculosis treatment failure prediction and identification of features

2.2 Features Identification Approaches

Following are some studies which focuses on features that can cause TB treatment to fail and risk factors of tuberculosis:

The study proposed in [26] focused on treatment failure of pulmonary TB and the factors responsible in BurkinaFaso (West African Country). Questionnaire was distributed among 100 patients and 100 control subjects to compare positive smear patients with negative smear control for the identification of exposure.

The WHO goal was to improve the quality and effectiveness of DOTS. It was needed to develop a tool to discover more severe cases so that DOTS can be applied more progressively. In the study [36] logistic regression model was used for prediction of treatment failure so that proper support is provided to patient as needed. Author used correlation coefficient, P value and logistic regression on 2005 data of Iran health system of all TB patients. Identified predictors were age, sex, nationality, weight history of TB cases and imprisonment. The system has shown accuracy of 81.64% on test data.

In [37] author find out the possible risk factors for the TB treatment failure and characteristics of patients failing treatment in south Korea. The radiographic, clinical, demographic and microbiological data was collected by interviews with the Tb specialist nurses. 52 patients of Tb treatment failure were selected and same number of patients with successful treatment were selected for comparison. It was found that previous tuberculosis history, diabetes and cavity were identified as risk factors for treatment failure. Medical support was found out as a supporting factor in success of treatment(AUC:0.79), however young age, low body mass index and tuberculosis history was found out in favor of poor compliance of patients(AUC:0.76). Low BMI, lung disease, diabetes, positive sputum AFB smear and MDR-TB were found in association with presence of cavities. All the risk factors associated with cavities and poor compliance must be avoided to increase rate of successful treatment.

The study [38] was focused on identification of factors associated with unfavorable treatment outcomes of extrapulmonary tuberculosis patients. Multivariate binary logistic regression analysis was used for this purpose. The research was conducted on 651 patients in Bahawalpur, Pakistan based on assessment of clinical forms and treatment outcomes. 177 patients had unfavorable treatment outcome out of which 10 patients died while 165 didn't follow up the treatment. The factors associated with unfavorable treatment outcome of extrapulmonary patients were Lymph node TB with (CI 0.422, 0.989 AOR 0.65, 95%) and Meningeal TB with (CI 1.065, 4.144 AOR 2.1, 95%). A large number of patients lost the follow up of treatment and success rate of treatment was less than the target set by world health organization (WHO) i.e 90%

The study [39] was focused on identification of factors associated with unfavorable treatment outcome of pulmonary tuberculosis patients including smear positive and smear negative. The study comprised of data of 22, 998 patients of Anqing, China. Non conditional logistic regression was performed on data. After detailed analysis it was found that factors associated with unfavorable treatment outcome of smear positive patients were unchecked chest x-ray, military shadow in chest x-ray, age above 35 years, cavity in chest x-ray, self medication treatment model and supervision in intensive phase where for smear negative patients, the factors were age above 45 years, delay over 51 days, unchecked chest x-ray, full course treatment management model and military shadow in x-ray.

Longer treatment time of drug resistant tuberculosis often results in poor treatment outcome including death. The research [40] was conducted on drug resistant tuberculosis patients in Ethiopia to predict time to poor treatment outcome. The research included 508 patients with median age of 28.5 years. It was found that after one year the cumulative survival probability of patients was 79%. HIV negative, rural residency, non-diabetic, secondary and above level education, non-anemic, without clinical compilations and rate of body change were identified as predictors for time to poor treatment outcome. Therefore these predicting factors of patients must be improved to increase survival time.

TABLE 2.1: Comparative analysis and evaluation of factors which results in TB treatment failure

Ref#	Method/ Technique	Evaluation parameters		Contribution	Limitations	Future Direction
[26]				Factors associated with pulmonary TB failure for evidence-based intervention in four regions of Burkina Faso	Delay of at least 1 year of research and interviews and health-care variables have not been identified.	Identify specific challenges to the health center in order to achieve success with high rates of TB treatment and improve TB compliance
[36]	Logistic Regression	**Train Accuracy** 0.821	**Test Accuracy** 0.816	A reliable model using patient data to identify the likelihood of the respective risk of failure at the beginning of DOTS therapy in order to provide patient monitoring and status-based support.	The features are only Demographic	
[37]	Logistic Regression	**AUC** 0.79		The purpose of our study is to characterize patients who are not receiving tuberculosis treatment, and to use national data to recognize risk elements for treatment failure and non-acceptance.	he dataset was too small	Larger studies are required to approve the findings.
[46]	Non Conditional Logistic Regression			The aim of the study was to identify factors related with clinical treatment outcome of tuberculosis patients including smear positive and smear negative.	It didn't represent all Tuberculosis Patients as it investigated new PTB patients. Missed socioeconomic data like lower income etc. Some other factors like compliance with treatment etc. were missing.	Some potential factors can be included to find their impact on data.
[38]	Kalper-Mier			The study was conducted on drug resistance tuberculosis to predict time to poor treatment outcome. This study estimates the time of treatment failure, which was described as the percentage of all patients who did not receive treatment or died, and patients getting second line anti-TB treatment.	The study based on secondary data, It missed some factors like radiological findings, socio-economic status etc.	Potential factors which were missing can be included to find their impact on data.

2.3 Machine Learning Approaches

Following are some researched which used machine learning model to predict TB treatment failure by using different features.

Feature selection is used to reduce the set of features to more important, relevant and sufficient ones. In the proposed study [25] author used feature selection techniques (forward stepwise selection, backward elimination, random forest, backward Stepwise elimination and LASSO) method to reduce the features from 23 to 5 along with prediction and also compared results with other prediction models like random forest, forward stepwise selection, SVM Linear Kernel, SVM Polynomial Kernel. Author used sensitivity, specificity, accuracy and misclassification as evaluation matrices. It was found that machine learning techniques are useful to predict treatment failure in TB. Most models accomplished AUC below or more than 0.7. Author doubted that the model might also be affected by the insufficient quantity of data and the results are needed to be validated on larger dataset.

Machine learning techniques are ascertained to be useful in finding association between attributes which can affect the result of any disease. The study [24] focuses on the features which are related with treatment failure. The dataset of 6 different countries has been used. Mutual information, Recursive feature elimination and univariate feature selection technique are used for selecting features. ANN, support vector machine, K-nearest neighbor, random forest and j48 classifiers are used. Machine learning method as useful in predicting with the accuracy of 78% overall and 92% on Romania's data. Features for all countries are also included in the study.

[32] Tuberculosis is major issue in public health. TB is treatable but if after the treatment patient doesn't care for health then it can become a worst form of tuberculosis which is drug-resistant tuberculosis. DOTS treatment is an efficient way to handle growth of tuberculosis in high burdened countries, but its economy dependent. The goal is to predict the treatment result at the start of the treatment to guarantee the efficient use of healthcare staff. At the beginning of the procedure,

the outcome is predicted so the method would be better and cost-effectively. Author used filling missing values, unit standardization, and discretization (clustering and binnig) for processing. For feature selecting author used p-value, chi- square test. After processing author used neural network (NN), random forest (RF) and support vector machine (SVM) with accuracies of 73, 74 and 76 respectively.

[31] Correct and rapid determination of mycobacterium tuberculosis (MTB) resistance against available tuberculosis (TB) drugs is essential for the control and management of TB. In this study author developed machine learning models to classify MTB resistance against eight anti-TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, ciprofloxacin, moxifloxacin, ofloxacin, streptomycin) and to classify multi-drug resistance. Author used LR and SVM, RF, PM, CBMM. Evaluation matrices are AUC, sensitivity and specificity. Compared to previous researches the result was improved in this paper. The model developed in this paper was not validated on Global samples.

It has been observed that 60-80% patients in developing countries and 25-30% patients do not complete their TB treatment process [41] resulting in evolving of bacterium to multi-drug resistant. Treatment therapy for MDR is more expensive so there is a need to predict the treatment outcome. Data has been gathered from multiple sources like health nurses, physicians etc. Bi-variate correlation is applied on the data to remove unrelated features. Six different models are applied on the dataset which has been divided to 70:30 ratio for training and testing. The models used are Logistic Regression(accuracy: 74%), Decision tree(accuracy: 62%), artificial neural network(accuracy: 58%), Radial basis function(accuracy: 58%), Bayesian network(accuracy: 54%) and Support vector machine(Accuracy: 57%).

Multi Drug resistant tuberculosis is a type of drug resistant which is resistant to some of drugs used for treatment of simple TB such as rifampicin and isoniazid. Several techniques were being used to deal with MDR-TB such as ML based prediction, DOTS and genome sequencing. The research [42] used different models like extra tree, adaboost, decision tree, random forest and linear regression. Data

cleaning is used for preprocessing. Adaboost provided the highest accuracy of 56.7%.

TABLE 2.2: Comparative analysis and evaluation of machine learning techniques used for TB treatment failure

Ref#	Method/ Technique	Evaluation parameters				Contribution	Limitations	Future Direction
		AUC	**Mis-Class**	**R**	**S**			
[24]	Forward stepwise selection	0.74	0.24	0.36	0.89	Treatment failure prediction and feature selection on a multi-country dataset	Missing data may have influenced the predictive capacity of the models	More variables and cases that also boost predictive performance with the NIAID Tuberculosis dataset.
	Backward stepwise elimination	0.73	0.27	0.3	0.88			
	Backwards elimination and forward stepwise selection	0.73	0.27	0.30	0.88			
	LASSO	0.72	0.23	0.21	0.96			
	Random Forest	0.70	0.24	0.30	0.91			
	SVM Linear kernel	0.69	0.24	0.21	0.94			
	SVM polynomial kernel	0.69	0.25	0	1			
[23]			**Ac**			Selection of features that are related to treatment failure	Generalize feature set is no mentioned as features are influencing differently on countries	Highest accuracy might improve by adding more features in feature set
	ANN		0.78					
	K-NN		0.73					
	RF		0.75					
	SVM		0.71					
	J48		0.7					
[31]		**Ac**	**P**	**R**	**S**	Predicting the outcome of the treatment of a particular patient at the start of treatment so that their health workers can be utilized in a targeted and cost- effective way.	The method used is very basic and advanced algorithms are available. And past TB diagnosis, specifics of patient immigration and patient awareness of the disease are needed for the study, etc.	Add some more specific factors for getting more accuracy.
	SVM (Support Vector Machine)	74	71	44	90			
	Random Forest	76	68	62	84			
	Neural Network	73	48	66	76			

Ref#	Method/ Technique	Evaluation parameters				Contribution	Limitations	Future Direction
[31]	LR and SVM RF PM CBMM	AUC Sensitivity Specificity				Development of machine learning model to classify MTB resistance against eight anti-TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, ciprofloxacin, moxifloxacin, ofloxacin, streptomycin) and to classify multi-drug resistance.	Use of Machine Leaning model on DNA sequencing data	The model can be Validated on global samples
[38]	Random Forest(RF) LstmrEal-time Adherence Predictor (LEAP)	**Ac** 0.72 0.74				Predicting the outcome of the treatment of a particular patient at the start of treatment so that their health workers can be utilized in a targeted and cost-effective way.	The method used is very basic and advanced algorithms are available. And past TB diagnosis, specifics of patient immigration and patient awareness of the disease are needed for the study, etc.	Add some more specific factors for getting more accuracy.
[40]		**Ac**	**F1**	**P**	**R**	Prediction of the outcome of the treatment or DOTS therapy for a new or relapse patient. That enhance the quality of DOTS therapy.	The models are only trained and tested on only one country dataset. And the factors are also limited	
	Decision Tree	0.62	0.74	0.75	0.74			
	Bayesian Networks	0.54	0.62	0.66	0.62			
	Logistic Regression	0.74	0.57	0.62	0.57			
	Multi-Layer Perceptron	0.58	0.57	0.67	0.57			
	Radial Basis Function	0.58	0.53	0.55	0.53			
	Support Vector Machine	0.57	0.50	0.62	0.51			
		Ac				MDR-TB prediction has widely been used in different machine learning method.		
	Logistic Regression	0.49						
	Decision Tree	0.40						
	Random Forest	0.50						
	Extra Tree	0.433						
	Adaboost	0.567						

Note: Ac = Accuracy P= Precision R= Recall S=Specificity

2.4 Deep Learning Approaches

Following are some researches which used Deep learning models to predict Drug resistance Tuberculosis and TB treatment failure.

This research [6] has used computer tomography images of lungs to predict multi-drug resistance. They adopted a patch based CNN model and SVM as classifier. CT images captures the abnormities only in limited region therefore patch based model is used. Their best results are showing accuracy of 91%. The results are very accurate; however, they are using a very small dataset of only 230 people. They are also using dataset of Drug Sensitive patients so results might be not that much reliable for other patients. Also, they are only using CT images of lungs only and no other feature is considered.

The paper [33] is using whole genome sequencing data in predication of most severe forms of TB MDR and XDR. They collected genotypic data of 3601 mycobacterium strains out of which 1228 were drug resistant. They used first time wide and deep neural network for this purpose. They sensitivity and specificity are shown in results separately for first line drugs and second line drugs. The performance is very good as compared to traditional approaches. We can see that specificity is increased for second line drugs but sensitivity is decreased and reduces greatly when independent dataset is used. The research is limited to only genotypic data and other features are not considered. This type of model can be used with other feature also to increase the performance considering demographic differences.

[43] In many locations, there is lack of expertise in radiology interpretation which could have false screening results. An automated approach could help in the screening evaluation process in the developing countries for the early detection of the TB. Author proposed use of Deep CNN (AlexNet and GoogLeNet) for the recognition of TB using chest radiography. Untrained and pre-trained networks were used to classify images. Dataset was collected from four different organizations, 68% data was used for training, 17.1% for validation and other for testing.

Networks were merged based on their high performance which gives 0.99 AUC, 97.3 sensitivity and 100% specificity.

The aim of the study [44] was to know whether there exist any feature related to risk of poor treatment outcome in observations of CT images by radiologist. Author used five different models featureless, logisticr regression, multinomial log regression, random forest and KNN. Each of the mentioned model is also evaluated under class balancing, no class balancing and smote. Dataset of 3rd Quarter of 2020 was collected from TB portal website. Author used 25% data as validation data to compare the performance of cox proportional hazards, Kaplan-Meier, and random forest survival model based on Harrell's C metric.

Deep Learning Models are used for the detection of pulmonary Tuberculosis. In the study [45] author compared three different Deep Learning Systems which are Lunit, CAD4TB and qXR. Data of 1196 patients (Cameron: 681, Nepal:515) was used. Two groups (DL systems and radiologist) read the CXR and gave Xpert MTB/RIF. AUC was similar for all system when Xpert was used as referenced standard. Us of DL systems for reading CXRs could help tp reduce the Xpert MTB/RIF tests required by 66% with sensitivity at 95% or better.

TABLE 2.3: Comparative analysis and evaluation of deep learning techniques

Ref#	Method/Technique	Evaluation parameters		Contribution	Limitations	Future Direction
		Accuracy in patch	**Accuracy in Subject**			
[6]	CNN + orderless pooling + SVM + slice		0.647	This research investigates MDR patient and drug-sensitive patients from CT lung images.	The dataset used in this paper consist only 230 records.	Need to embed medical knowledge like MDR disease pattern to get high accuracy. To improve characteristics of 3D dataset, 3D segments should also be taken to consideration.
	CNN + patch	0.793	0.844			
	Alexnet with Softmax + patch	0.796	0.911			
	Dense SIFT + SVM +patch	0.835	0.888			
	CNN + SVM + patch	0.798	0.911			

Ref#	Method/Technique	Evaluation parameters			Contribution	Limitations	Future Direction
		Accuracy First Line Drug	**Accuracy 2nd Line Drug**				
[33]	MLP (Select Mutations)	0.979	0.934		Identification of multidrug resistant tuberculosis using multitask deep learning model.	Only sequencing data was used	
	Multitask WDNN	0.979	0.937				
	Random Forest	0.972	0.937				
	Logistic Regression (Preselected Mutation)	0.971	0.887				
	Logistic Regression (Common Mutation)	0.969	0.902				
	SD WDNN	0.978	0.928				
		R	**S**				
	WDNN	0.843	0.910				
	Logistic Regression	0.811	0.898				
[43]		**AUC**	**R**	**S**	To calculate the usefulness of DCNNs for discovering tuberculosis (TB) on chest radiographs	Over fitting results in loss of data.	
	AlexNet-TA	0.98	0.92	0.947			
	GoogLeNet-TA	0.98	0.92	0.987			
	Ensemble-TA	0.99	0.97	0.947			
[45]		**Ac**	**R**	**S**	Use of Deep Learning Systems to detect chest radiography abnormalities	They didn't consider Xpert as reference standard despite WHO recommendation due to potential biasness of Xpert.	Performance can be improved by checking systems with more data.
	CAD4TB	0.92	0.47	0.96			
	Lunit	0.94	0.58	0.97			
	qXR	0.94	0.71	0.96			

Ref#	Method/ Technique	Evaluation parameters				Contribution	Limitations	Future Direction
	No Class Balancing							
		Ac	**AUC**	**R**	**S**			
	Featureless	0.91	0.50	1.00	0.00			
	Logistic Regression	0.91	0.72	1.00	0.00			
	Multinomial Log Regression	0.91	0.76	1.00	0.00			
	Random Forest	0.91	0.84	1.00	0.00			
	KKnn	0.91	0.71	1.00	0.00			
	Class Balancing							
		Ac	**AUC**	**R**	**S**			
	Featureless	0.45	0.50	0.47	0.33	The aim of the study was to know whether there exist any feature related to risk of poor treatment outcome in observations of CT images by radiologist.	The model cannot be used for the prediction of intermediary end point treatment. E.g Failure among two extremes (cured/died).	
	Logistic Regression	0.67	0.80	0.64	1.00			
[44]	Multinomial Log Regression	0.66	0.82	0.62	1.00			
	Random Forest	0.69	0.82	0.66	1.00			
	KKnn	0.78	0.76	0.81	0.50			
	SMOTE							
		Ac	**AUC**	**R**	**S**			
	Featureless	0.09	0.50	0.00	1.00			
	Logistic Regression	0.53	0.73	0.48	1.00			
	Multinomial Log Regression	0.53	0.75	0.48	1.00			
	Random Forest	0.69	0.74	0.69	0.67			
	KKnn	0.92	0.70	1.00	0.17			
	RBF(Radial Basis Function)	0.79	0.53	0.55	0.53			
	SVM(Support Vector Machine)	0.76	0.50	0.62	0.51			

Note: Ac= Accuracy P=Precision R=Recall S=Specificity

TABLE 2.4: Dataset description for tuberculosis treatment failure

Ref	Source of Dataset and Links	No.of Records	Attributes	Benchmark
[24]	National Institute of Allergy and Infectious Disease, Maryland	1533	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23	Artificial Neural Network 0.78 Accuracy
[25]	National Institute of Allergy and Infectious Disease, Maryland	587	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23	Forward stepwise selection 0.74 Accuracy 0.36 Sensitivity
[6]	ImageCLEF 2017 competition	230	CT Lungs Images	CNN + SVM + patch 0.91 Accuracy
[33]	WHO network of supranational reference laboratories and the ReSeq TB knowledgebase	3,601 Mycobacterium tuberculosis strains	Sequence Data	Wide and deep neural network (WDNN) 1st Line Drug: Sensitivity:0.927 Specificity:0.927 2nd Line Drug: Sensitivity:0.845 Specificity:0.936

[31]	MTB	1839	41	0.87 Sensitivity
[32]	Years 2011 and 2014 for TB Reach projects.	4213		Random Forest 0.76
[43]	National Institutes of Health (Maryland, and Shenzhen, China) Thomas Jefferson University Hospital Belarus TB public health program	1007	Chest Radiography	Ensemble-TA 0.99 AUC
[44]	TB Portal Website	4300	CT Images	KKnn 0.92 Accuracy
[36]	Registered TB patients in health system of Iran 2005	4836	2, 3, 4, 5, 33, 25	Logistics Regression 0.816 Accuracy
[45]	B.P. Koirala Institute of Health Sciences (BPKIHS) Bamenda and the Bamenda Regional Hospital in Cameroon	1196	CXR Images	Lunit, qXr 0.94 Accuracy
[40]	Gondar Comprehensive Specialized Hospital, Boru-Meda Hospital, and Debre-Markos Referral Hospital	508	socio-demographic clinical, behavioural variable	

2.5 Research Gap

In TB treatment failure prediction more relevant features need to be focused such as Genmic, X-rays along with clinical and Demographic as highlighted in [33, 42-44] that can contribute to predict treatment failure types such as failure with resistance, failure without resistance, resistance with types (mono, poly, MDR, XDR etc). The studies included in literature have ignored these vital features of Genomic and Xrays, by adding these features to predict muti-class treatement prediction become more complicated and complex to compute the generalized set of features which are more useful and essential for treatment failure prediction. Deep learning models (CNN, AlexNet, GoogLeNet etc) are proven to be suitable choice in literature review to solve both issues, of handing varieties of features with respect to demographics and generate better results as compared to machine learning model. Although the existing datasets are small for experimental purpose and we are planning to utilize a standard benchmarks dataset from NIH, USA including more than 151 features of 2441 patients.

Summary

This chapter discusses the different researches which were conducted to tackle the problems of Tuberculosis. The chapter summarizes the researches comprising of different machine learning and deep learning models for prediction of Tuberculosis treatment failure. Different experiments were also conducted to retrieve the most effective features set. Each study used specific set of features to train and test the relevant models. The studies usually predict binary outcome (failure, not failure).

Chapter 3

Problem Statement

This chapter discusses the identified problem and methodology to predict the TB treatment failure. Therefore, section 3.1 of this chapter explains the problem statement. Section 3.2 discusses research questions. Section 3.3 explains objectives of this research. Section 3.4 shows the methodology used in this research. Section 3.5 discusses the explanation the methodology.

3.1 Problem Statement

This study utilized more enrich multisource features set comprises of Demographic (Gender, Country, Education level, Employment status etc), Clinical (Pleaural effusion, Nodal Calcinosis, Pleuritis, Pneumothorax etc), Xray (status, peffusion, cavity, nodule, atelectasis etc) and Genomic (genename, genexpert, letest, haintest etc) for the prediction of multilabel tuberculosis treatment failure as "No Failure", Failure with Resistance" and "Failure without Resistance".

3.2 Research Questions

1. **Can the genome and x-rays feature set contribute to predict TB failure along clinical and demographic features?**

Yes. Section 5.5.4 shows the impact of using genome and x-ray features along with clinical and demographics features.

2. **Can Deep Learning models be more efficient and accurate for TB failure prediction as compared to previously proposed machine learning techniques?**
   Yes, as compared to previously proposed approaches, CNN provides improved results on complete feature set (section 5.1.3.1) but in this study another method of machine learning, random forest provides almost equivalent results on reduced feature set (section 5.1.2.2).

3. **Can we be able to identify the generalized set of features from various data sources for the prediction of TB treatment failure?**
   Yes, see section 4.5 for generalized feature set and section 5.1.2 for the results on generalized feature set.

3.3 Objectives of the Research

1. To identify the impact of genome and x-ray sources along with clinical and demographic information of TB patient to predict the treatment failure.

2. To identify the suitable feature sets by applying various scientific methods like Info Gain, Ranking etc and to classify multi label prediction of treatment failure.

3. Through various extensive experiments to identify the generalized set of features of different localities based upon the multi-source data.

3.4 Research Methodology

The focus of this study is to search the factors that contribute in treatment failure in TB (tuberculosis) and then on the basis of those factors predict the treatment

failure in TB (tuberculosis). The goal of this study is to reduce the mortality of the tuberculosis patients. The literature is an organized in conceptual order. Figure 3.1 shows the research methodology. Major steps of the methodology will be as follows:

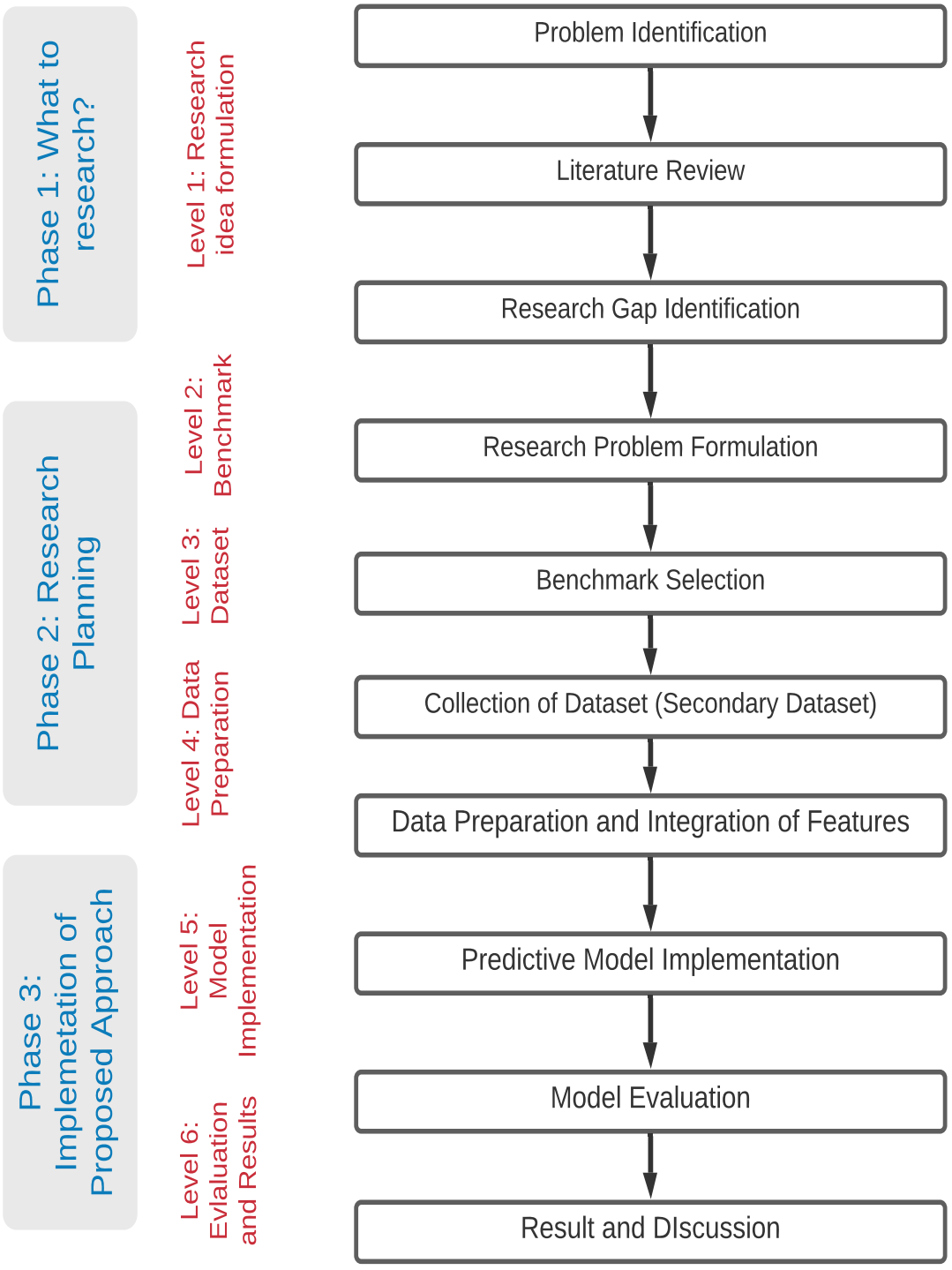


FIGURE 3.1: Proposed research methodology for prediction of TB treatment failure.

3.5 Explanation of Methodology

Methodology is divided into three different phases. Phases 1 includes research idea formulation. In phase 2 research planning (benchmark, dataset and data preparation) has been done. In phase 3iImplementation and evaluation has been done. Detailed methodology is explained below.

3.5.1 Problem Identification

TB treatment failure prediction is a challenging area in treatment domain where various features from multiple sources can contribute to predict various failure types such as failure with resistance, failure without resistance, resistance with types (mono, poly, MDR, XDR etc) which make this challenge more complicated and complex to computer the generalized set of features which are more useful and essential for prediction of treatment failure.

3.5.2 Literature Review

Literature is divided into three sections. There are studies which involve on identifying the features which can cause TB treatment failure [26, 36, 37, 40]. Other studies apply different sources of features to predict treatment failure using machine learning Models [24, 25, 31, 32, 41, 42, 46]. Due to diversity and complexity of features some studies used Deep Learning model for the prediction of Tuberculosis and its treatment [6, 33, 43–45].

3.5.3 Research Gap Identification

From the literature it is concluded that:

- More relevant features need to be focused such as genomic and c-Rays

- Data needs to be balanced
- Deep Learning models might be more suitable with multi-scourse, multi-class data to avoid feature selection as a separate step

3.5.4 Dataset

Dataset consist of 151 features of approximately 2441 patients. Data include 24 demographic and clinical Features, 55 x-ray and CT features, 71 genomic and sequenced data features.

3.5.5 Data Preparation and Integration

Data of different features was integrated using ID of the patients. Raw data was prepared and filtered for training using Data Mining Tool (Weka).

3.5.6 Predictive Model Implementation

For machine learning model, data mining tool (Weka) is used. Deep learning models are implemented in python.

3.5.7 Evaluation

Through various extensive experiments to identify the generalized set of features of different localities based upon the multi-source data. Evaluation matrices will be recall and accuracy.

- **Precision**

It represents the percentage of correctly classified instances by total number of instances that are real positive. In case of imbalanced classes, precision calculates

the accuracy of minority class. It is calculated by formula

$$Recall = \frac{tp}{tp + fp} \tag{3.1}$$

- **Recall**

It represents what percentage of actual positives are predicted by the model. In case of imbalanced data, recall measures the coverage of minority class. It is denoted by formula

$$Recall = \frac{tp}{tp + fn} \tag{3.2}$$

- **Accuracy**

It represents proportion of accurate prediction to the total of test data entities and denoted by formula:

$$A = \frac{tp + tn}{tp + fp + fn + tn} \tag{3.3}$$

- **F-Measure**

It is Harmonic mean of recall and precision. It is really suitable for imbalanced classes which weights both precision and recall equally. It is denoted by formula:

$$A = 2 * \frac{precision * recall}{precision + recall} \tag{3.4}$$

TABLE 3.1: Confusion matrix

		Predicted Classes	
		Positive	**Negative**
Actual Class	**Positive**	True Positive	False Positive
	Negative	False Negative	True Negative

3.5.8 Tools and Programming Languages

1. **Weka** is used for feature selection and machine learning models.
2. **Python** is used to implement Deep Learning Models (CNN and Alexnet).
3. **Microsoft Excel** is used to store dataset and results.
4. **Jypyter Notebook** is used to create and share computational document.

Summary

This chapter mentions the three problems derived after the detailed literature review which are absence of x-ray and genomic features, no generalized feature set and no multi label outcome prediction. The chapter illustrates the detailed methodology to solve the discovered problems. The data set comprises of 151 features of approximately 2441 patients including xray and genomic features. For evaluation, precision, recall, accuracy and f-measure will be used.

Chapter 4

Proposed Approach for Tuberculosis Treatment Failure

This chapter discusses the details of proposed approach "Predictive Approach for Tuberculosis Treatment Failure using Patients Multisource Data of Drug Resistance (TFMDR) ", to achieve objectives of study. Therefore, section 4.1 of this chapter explains the description of dataset. Section 4.2 discusses pre-processing steps (format correction, fill in missing values, normalization) which were performed on data to prepare it for model. Section 4.3 explains techniques used to solve class balancing problem which are class balancer and SMOTE. Section 4.4 explains the feature selection techniques used in this study. Section 4.5 discusses the feature selected for the study using ranking (Boruta) and infoGain method. Section 4.6 discussed classification techniques used for this research.

The existing studies used only clinical and demographic data to predict TB treatment failure in binary class as failure or not failure. This study utilized more enrich feature such as clinical, demographic, genomic and x-rays to predict multilabel tuberculosis treatment failure.Study used Machine learning models (random forest, decision tree, SVM and KNN) and deep learning models (CNN and alexNet). The proposed research approach (TFMDR) is shown in Figure 4.1.

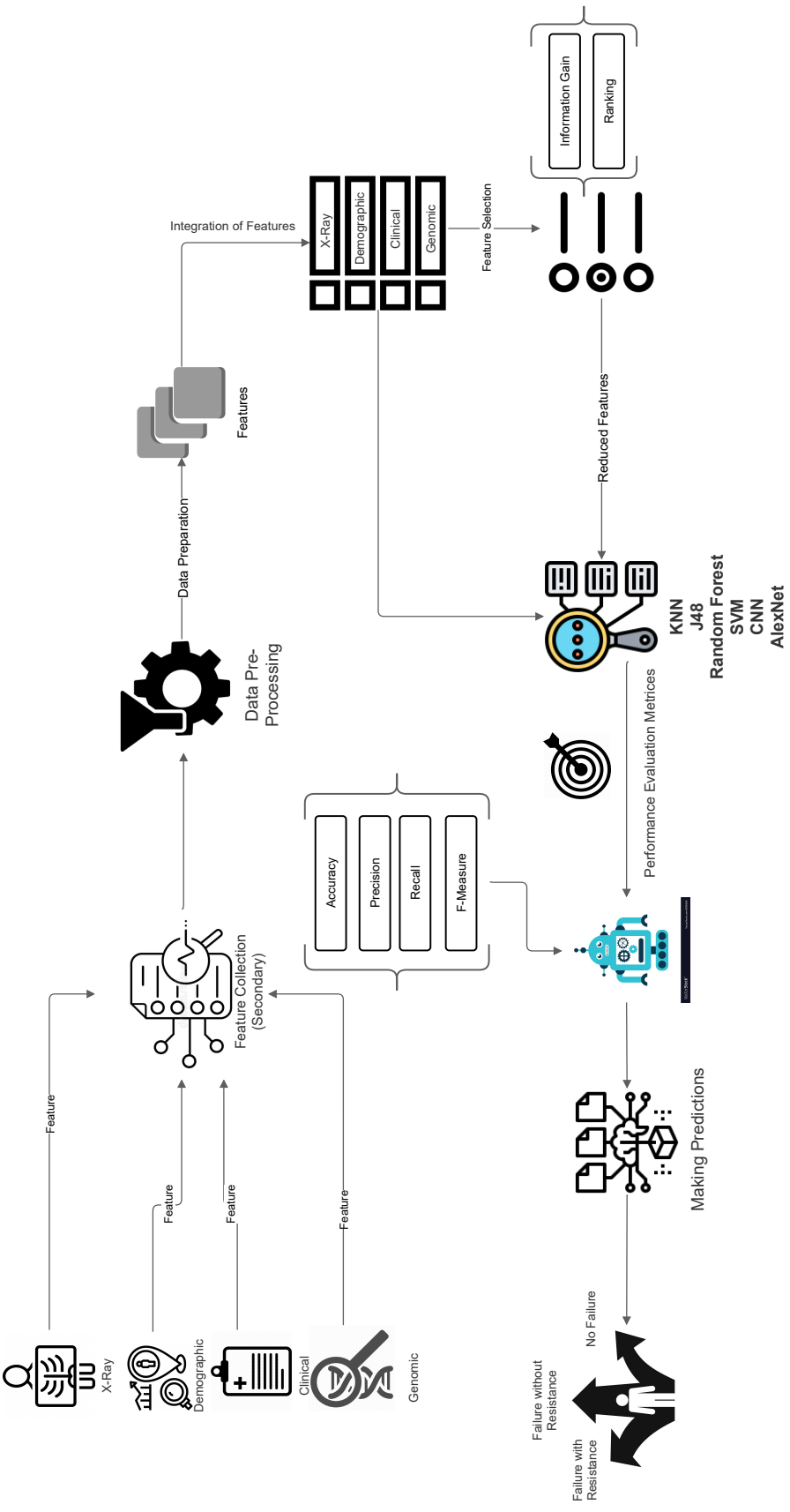


FIGURE 4.1: Proposed approach for tuberculosis treatment failure

Architecture to obtain results compromises of following steps.

4.1 Dataset Description

The OCICB (Cyber Infrastructure and Computational Biology) Department developed by the TB portal programs under the NIAID (National Institute for Allergy and Infectious Diseases) is a worldwide partnership for the distribution of TB data for research expansion. Clinicians and researchers are contributing with data scientists to collect multi-domain data of tuberculosis and to share it with researchers to advance the research in tuberculosis domain. Tuberculosis portal give access to database which include genetic, demographic, clinical, imaging and other information of patients from numerous countries around the globe. The dataset comprises of 2441 instances of three classes (no failure, failure with resistance and failure without failure) which contains patients' data from 7 countries which are Azerbaijan, Georgia, Belarus, Kazakhstan, Moldova, Nigeria, Romania. The data is available on Tuberculosis portals (https:/depot.tbportals.niaid.nih.gov). The database is modified with time. Data used in this research is from start to May 2021. The selected attribute is treatment failure that is identified as therapy failure or death. The variables from different categories (demographic, clinical, genomic, x-ray, CT) are used in the prediction. Table 4.1 shows the description of dataset.

TABLE 4.1: Dataset description

Data	**Count**
Total Instances	2441
Total Features	151
Classes	3
Countries	7

4.2 Pre-processing

Data accessed from TB portals is raw and contain anomalies. In training stage it is really hard to trace information from redundant and irrelevant data. Preparation and filtration of data is somehow time taking procedure.

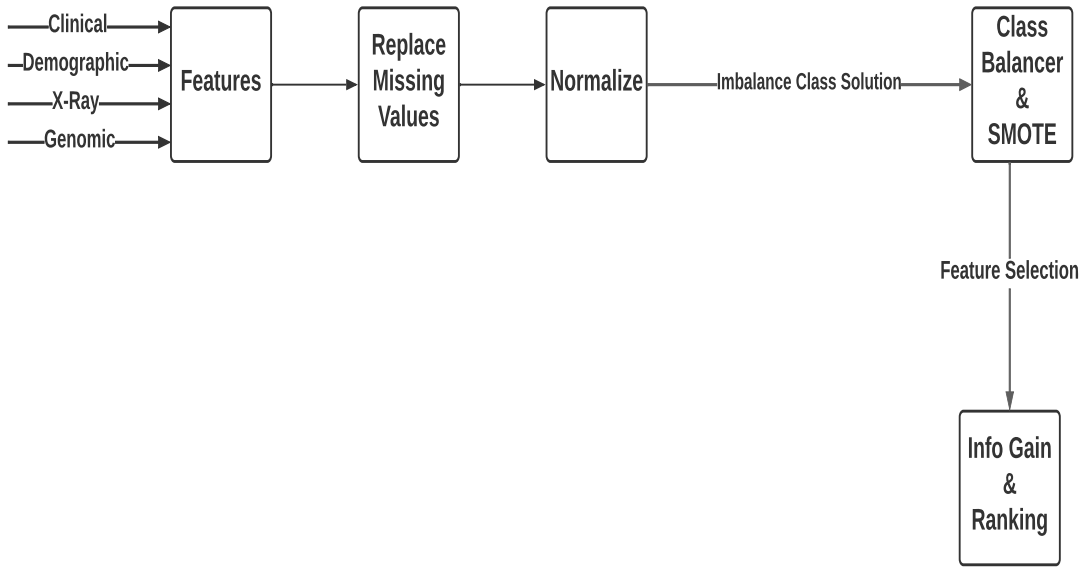


FIGURE 4.2: Data pre-processing

For preparing the data for experimentation, various pre-processing steps have been followed.

4.2.1 Format Correction

Few features in the dataset have both integer as well as string values which are causing error in the training process; therefore, all the integer values are replaced with string values. For example in the pleuraleffusion_percent_of_hemithorax_involved column, there are values like less than 50, not reported, 0 etc, so all the 0 values are changed to "NO" to make the type of data consistent.

4.2.2 Fill in Missing Values

Some of the features also have empty spaces which is not a proper format for usage in data mining tool (Weka). So pre-processing filter named as ReplaceMissingValues in weka is used to fill in the missing data which is based on PMM (predictive mean matching) was used. Table 4.2 shows that features with count of missing values in dataset.

TABLE 4.2: Missing values in dataset

Feature Name	**Count**	**Percentage**
No of Children	1241	51%
No of Daily Contacts	665	27%
BMI	766	31%
Period End	58	2%
Period Span	58	2%

4.2.3 Normalization

For normalization of data the pre-processing filter named as Normalize in weka which uses min-max normalization technique was used.

4.3 Class Balancing

The dataset is very imbalanced as it contains 2054 no failure instances, 308 failure with resistance instances and 79 failure instances, therefore the classes were balanced with two techniques in weka which is class balancer and SMOTE.

4.3.1 Class Balancer

It is a technique in which equal weight is assigned to all classes. The total sum of weights beyond all instances will be maintained. Pre-prcoessing filter Class Balancer is applied for assigning weights to classes. Table 4.3 shows that weights assigned to each class after applying Class Balancer.

TABLE 4.3: Weights of classes after using class balancer

Class	Count	Weights
No Failure	2054	813.667
Failure with Resistance	308	813.667
Failure without Resistance	79	813.667

4.3.2 SMOTE

SMOTE is a tool that Weka uses to increase the minority group when such imbalance occurs. It is a Weka filter, and its use can increase classifier performance even if the dataset is imbalanced. Table 4.4 shows the number of instances of each class after applying SMOTE.

TABLE 4.4: Number of instances of each class after applying SMOTE

Class	Count	Count after applying SMOTE
No Failure	2054	2054
Failure with Resistance	308	2464
Failure without Resistance	79	2528

4.4 Feature Selection Techniques

Feature selection is a process of reducing features by selection the relevant ones for construction of model. In this process most consistent, relevant and non-redundant features are selected. Two techniques used in this research for feature selection are 1) Information Gain and 2) Boruta Ranker.

4.4.1 Information Gain

Information Gain splits the dataset according to some random variable's value. It selects feature by calculating the gain of variable with respect to target variable [47]. Information gain is calculated with the help of entropy. Entropy is impurity of collection of examples.

$$Entropy(S) = -plog(p) - qlog(q)$$

Here 'S' is collection of training examples, 'p' is proportion of positive examples and 'q' is proportion of negative examples

$$InfoGain(S, A) = Entropy(S) - \sum_{v \in values(A)} \frac{|S_v|}{|S|} Entrop(S_v)$$

A is the attribute relative to collection of example S.

4.4.2 Boruta

This algorithm selects feature by ranking them. It is based on random forest algorithm. It decides the importance of feature by ranking them. P value can be adjusted accordingly to adjust the strictness of algorithm. By default P value is 0.01. Maximum number of time the algorithm runs is denoted by maxRuns. Higher value of maxRuns provide more selective features. By default value of maxRuns is 100 [48].

4.5 Reduced Feature Set

The total combination of all the features is 150 which can contain many irrelevant features degrading the results, therefore it was needed to reduce the feature set to eliminate irrelevant features and decrease training time for model. Two techniques for feature selection which are infoGain and ranker were used to generate a reduced feature set of common features from both techniques. Table 4.5 shows the reduced feature set comprises of 27 features.

TABLE 4.5: Reduced features of TB data by ranking and infoGain method

Feature category	**Feature Name**
Clinical and Demographic	Country
	Case Definition
	Education
	Xray Count
	Start Period
	End Period
	Period Span
	Regimen Count
	Treatment Status
	Regimen Drug
	Comorbidity
	Xray exists
	Ct exists
	Genomic data exists
Xray	Affect Pleura
	Overall percent of abnormal volume
	Qure Consolidation
	Qure Peffusion
Genomic	Le Isoniazid
	Le Rifampicin
	Le p aminosalicylic acid
	Hain Isoniazid
	Hain Rifampicin
	Ncbi Bioproject
	Gene Name

4.6 Classification

Surprised Learning classifiers are used in this research. In supervised predetermined category is allocated on the bases of observers unknown. Training dataset is used to train machine learning models. It is labeled data which help program to learn and predict refined results. Classifiers are used to build model. Classifiers have their own algorithms which are used to perform classification. In classification predictive modeling input variables (X) are mapped to distinct output variables (Y). Aim is to identify the label of un-labeled data. Four machine learning models 1) Random Forest 2) Decision Tree (J48) 3) SVM and 4) KNN are used in this research.

4.6.1 Random Forest

It is a machine learning algorithm under supervised category that is built from decision tree algorithms. It produces various decision trees and ensemble them together to achieve more accurate and firm prediction [49]. It is mostly trained by bagging method that is combination of learning models that increase the overall results [50]. All trees contribute in the prediction of new class label. The label with highest number of votes will be allocated to new class. In this random sampling few samples may be unconsidered [51].

4.6.2 Decision Tree

It is a tree structure which is used for prediction and classification. It is a flowchart where internal nodes signify attribute's test, branches indicate an outcome of the test and leaf nodes represent the class label. Aim is to build a model that predicts the target variable value by studying decision rules deduced from data features. On the bases of test of attribute value, decision tree split source set into subsets. Same procedure is repeated with derived subsets in an iterative manner known as recursive portioning. This process remains continuous until portioning doesn't add

any value to prediction subsets of all node have similar value of target variable. Decision tree is suitable for experimental knowledge discovery because it doesn't need any domain knowledge. It can be used for high dimensional data. Decision tree can handle both number and categorial data. There are many types of decision tree in which ID3, C4.5, J48, MART and CHAID are included. ID3 was implemented in 1975. ID3 is known as Iterative Dichotomiser 3. It uses top-down greedy method. At each step it repeatedly divides features into two or more groups [52]. It is used for nominal features. ID3 uses InfoGain for evaluation. C4.5 is an extension of ID3 [53]. It was introduced in 1993 by Ross Quinlan. In c4.5 we find base first. For each C attribute InfoGain is calculated. Node with highest value is divided and then added to children node. J48 is improved version of c4.5. The result of j48 is a decision tree [47]. CART method was introduced in 1984. In this each node is divided into two nodes and child nodes are considered as parent [54]. CHAID method was introduced in 1980. It uses Chi-Square splitting method [55].

4.6.3 Support Vector Machine

SVM is most common supervised machine learning algorithm. It produces a mapping function output of given input using a labeled data instances [51]. It can be used for both regression and classification. Aim of SVM is fit the given data, execute the best fit hyper plane that classifies the given data. After receiving the hyper plane Features can be served to different classifier to get the predicted class. SVM uses one vs one technique for multi-classes [56].

4.6.4 K Nearest Neighbour

It is machine learning model under supervised category used for regression and classification. It supposes that alike things occur in close proximity. It calculates distance between data points. Euclidean distance and Manhattan distance are used to measure the distance [57].

4.6.5 Convolutional Neural Network

Convolutional neural network (CNN), a class of artificial neural networks in deep learning that has become dominant in various computer vision tasks, is attracting interest across a variety of domains, including radiology. In deep learning it is most commonly applied to analyze the visual imagery. As compared to other classical models, CNNs take image data, train the model, and then classify the features automatically for healthier classification [58]. CNN extract the each and every portion of input image through back propagation by using multiple building blocks, such as convolution layers, pooling layers, and fully connected layers. On the basis of these significant features it assigns weights for each neuron, so that it can discriminate the importance of neurons from one another. Using multiple filters Convolution operation is useful to extract features from the data set, to solve complex problems and generate feature maps. The subsampling pooling mechanism is used to reduce the dimensionality of feature maps from convolution operation, because a large set of feature can lead to overfitting [59].

4.6.6 AlexNet

AlexNet is 8 layer deep convolutional neural network. It can train millions of images and classify them into 1000 different classes. It contain five covolutional layers with max-pooling layers and three dense layers (fully connected layers). Softmax activation function is used in output layer. To reduce overfitting problem in AlexNet, Data Augmentation and Dropout is used. It contains 62.3 parameters in its architecture [60].

Summary

This chapter discusses the proposed research model in detail. First pre-processing steps have been applied on the retrieved data set which are format correction, filling missing values, and normalization. As there were more no failure cases and less failure cases therefore Class Balancer and Smote are used to tackle the class imbalance problem. Feature set is reduced from 151 to 27 using ranking and

info gain method. For classification, random forest, J48, SVM, KNN, CNN and AlexNet are used.

Chapter 5

Results and Discussion

In this chapter, tuberculosis treatment failure prediction approach will be evaluated. Data has been pre-processed to prepare it for experiments and then trained different machine learning and deep learning models using different feature sets. The aim is to compare the accuracy and F-measure under different setups.

5.1 Experiments

Different experiments were performed on dataset. Table 5.1 illustrates different experimental settings used in this approach.

Table 5.1: Experimental settings

No	Detail
Experimental Setting 1	ML Model with all features
Experimental Setting 2	ML Model with reduced features
Experimental Setting 3	Deep Learning Model with all features

5.1.1 ML Classification Results with All Features

5.1.1.1 Class Balancer

Figure 5.1 shows the classification results of different machine learning methods using class balancer to remove/ eliminate the class imbalance problem. The current experiment included all the available features. F-measure is use as evaluation metric. Figure 5.1 shows the F-measure of each class on different machine learning methods. Highest F-measure for all classes (no failure, failure with resistance and failure without resistance) is achieved by J48 which is 0.82, 0.871 and 0.908 respectively.

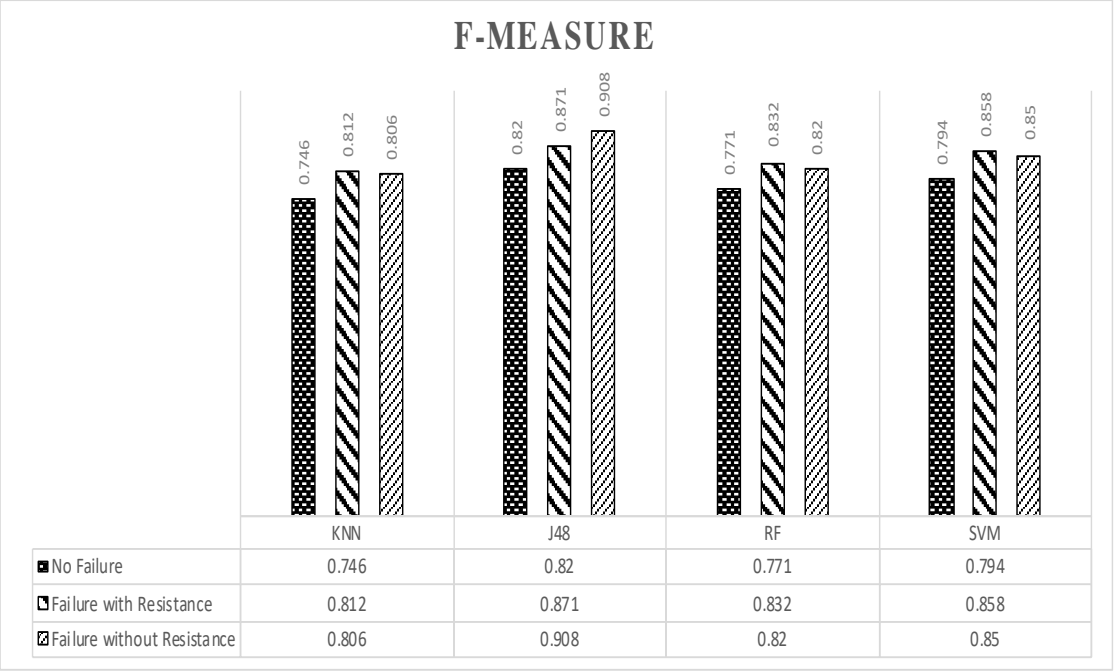


FIGURE 5.1: F-Measure comparison with different ML models using all features and class balancer

Table 5.2 shows the values of precision, recall, f-measure and accuracy class using all machine learning methods. Here the highest accuracy is achieved by J48 that is 0.865.

TABLE 5.2: ML classification results with all features using Class Balancer

	No Failure			Failure w Resist			Failure w/o Resist				
Models	**P**	**R**	**F1**	**P**	**R**	**F1**	**P**	**R**	**F1**	**Acc**	**F1**
KNN	0.61	0.96	0.75	0.96	0.71	0.81	0.98	0.68	0.81	0.782	0.79
J48	0.79	0.86	0.82	0.88	0.87	0.87	0.95	0.87	0.91	0.865	0.87
RF	0.65	0.96	0.77	0.94	0.75	0.83	0.97	0.71	0.82	0.803	0.80
SVM	0.68	0.96	0.79	0.95	0.78	0.86	0.99	0.75	0.85	0.829	0.83

*P= Precision, R=Recall, F1= F1-Measure, Acc=Accuracy

5.1.1.2 SMOTE

Figure 5.2 shows the classification results of different machine learning methods using SMOTE balancer to remove/ eliminate the class imbalance problem. The current experiment included all the available features. Figure 5.2 shows the F-measure of each class on different machine learning methods. Highest F-measure for all classes (no failure, Failure with resistance and Failure without resistance) is achieved by Random Forest which is 0.928, 0.955 and 0. 985 respectively.

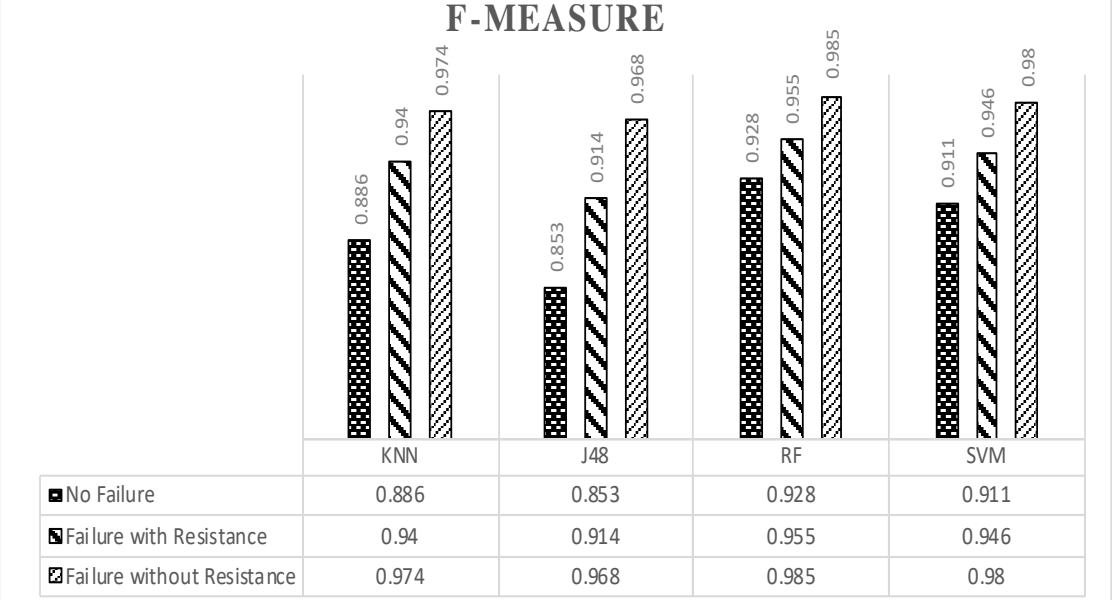


FIGURE 5.2: F-Measure comparison of all classes on different ML models using all features and SMOTE

Table 5.3 shows the values of precision, recall, f-measure and accuracy class using all machine learning methods. Here the highest accuracy is achieved by random forest that is 0.957.

TABLE 5.3: ML classification results with all features using SMOTE

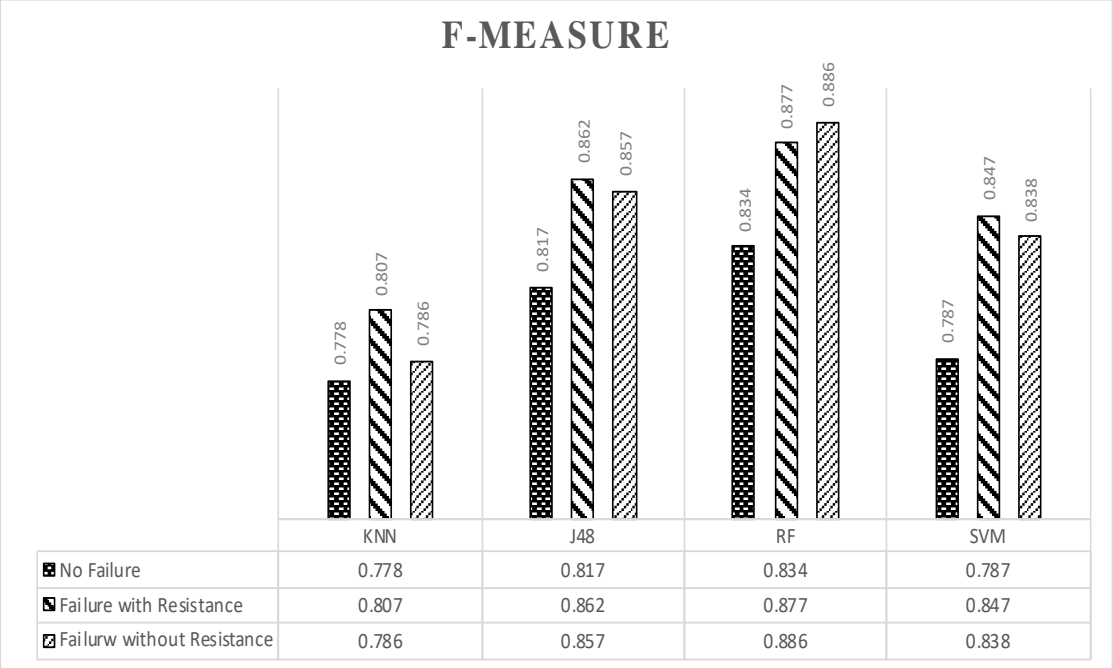
	No Failure			**Failure w Resist**			**Failure w/o Resist**				
Models	**P**	**R**	**F1**	**P**	**R**	**F1**	**P**	**R**	**F1**	**Acc**	**F1**
KNN	0.95	0.83	0.89	0.91	0.97	0.94	0.96	0.99	0.97	0.937	0.93
J48	0.98	0.82	0.85	0.90	0.93	0.91	0.96	0.98	0.97	0.916	0.91
RF	0.93	0.92	0.93	0.95	0.96	0.96	0.98	0.99	0.99	0.957	0.95
SVM	0.92	0.91	0.91	0.94	0.95	0.95	0.98	0.98	0.98	0.949	0.94

*P= Precision, R=Recall, F1= F1-Measure, Acc=Accuracy

5.1.2 ML Classification Results with Reduced Features

5.1.2.1 Class Balancer

Figure 5.3 shows the classification results of different machine learning methods using class balancer to remove/ eliminate the class imbalance problem. The current experiment included all reduced feature set. Figure 5.3 shows the F-measure of each class on different machine learning methods. Highest f-measure for all classes (no failure, failure with resistance and failure without resistance) is achieved by Random Forest which is 0.834, 0.877 and 0.886 respectively. 0.82, 0.871 and 0. 908 respectively. F-measure of no failure and Failure with resistance class is improved as compare to all features.



	KNN	J48	RF	SVM
No Failure	0.778	0.817	0.834	0.787
Failure with Resistance	0.807	0.862	0.877	0.847
Failurw without Resistance	0.786	0.857	0.886	0.838

FIGURE 5.3: F-Measure comparison of all classes on different ML models using reduced features and class balancer

Table 5.4 shows the values of precision, recall, f-measure and accuracy class using all machine learning methods. Here the highest accuracy is achieved by random forest that is 0.863.

TABLE 5.4: ML classification results with reduced features using class balancer

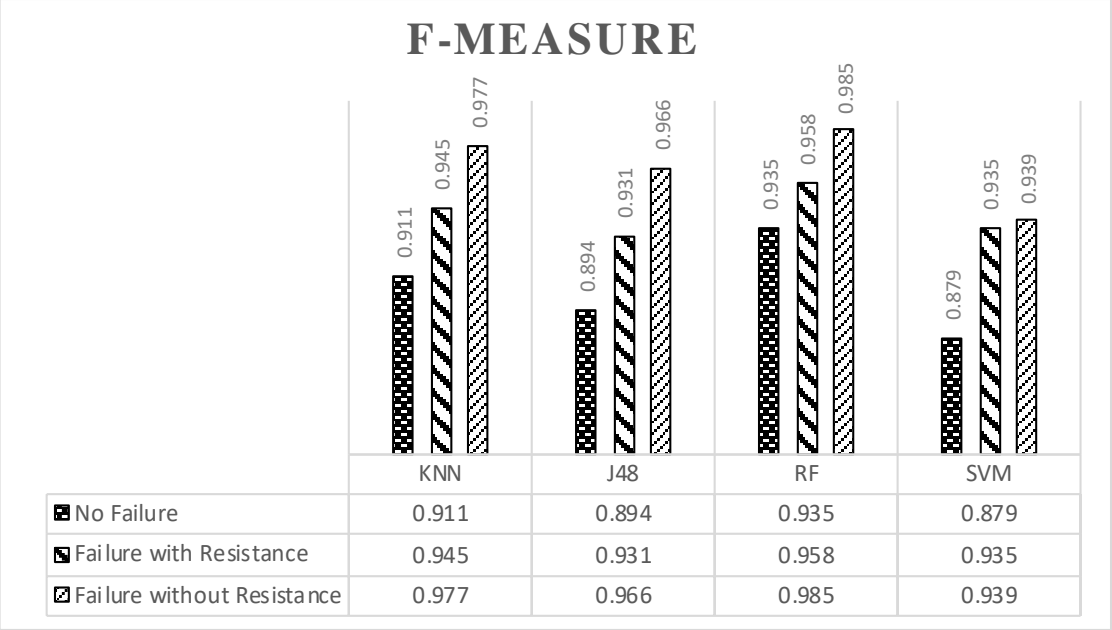
	No Failure			**Failure w Resist**			**Failure w/o Resist**				
Models	**P**	**R**	**F1**	**P**	**R**	**F1**	**P**	**R**	**F1**	**Acc**	**F1**
KNN	0.65	0.98	0.78	0.90	0.73	0.81	0.98	0.66	0.79	0.789	0.790
J48	0.77	0.87	0.82	0.86	0.87	0.86	0.93	0.80	0.86	0.844	0.845
RF	0.73	0.97	0.83	0.96	0.81	0.88	0.98	0.81	0.89	0.863	0.865
SVM	0.76	0.82	0.79	0.89	0.81	0.85	0.84	0.84	0.84	0.822	0.824

*P= Precision, R=Recall, F1= F1-Measure, Acc=Accuracy

5.1.2.2 SMOTE

Figure 5.4 shows the classification results of different machine learning methods using SMOTE to remove/ eliminate the class imbalance problem. The current

experiment included reduced feature set. Figure 5.4 shows the f-measure of each class on different machine learning methods. Highest f-measure for all classes (no failure, failure with resistance and failure without resistance) is achieved by random forest which is 0.935, 0.958 and 0.985 respectively. F-measure of no failure and failure with resistance class is improved as compare to all features.



	KNN	J48	RF	SVM
No Failure	0.911	0.894	0.935	0.879
Failure with Resistance	0.945	0.931	0.958	0.935
Failure without Resistance	0.977	0.966	0.985	0.939

FIGURE 5.4: F-Measure comparison of all classes on different ML models using reduced features and SMOTE

Table 5.5 shows the values of precision, recall, f-measure and accuracy class using all machine learning methods. Here the highest accuracy is achieved by random forest that is 0.961.

TABLE 5.5: ML classification results with reduced features using SMOTE

	No Failure			**Failure w Resist**			**Failure w/o Resist**				
Models	**P**	**R**	**F1**	**P**	**R**	**F1**	**P**	**R**	**F1**	**Acc**	**F1**
KNN	0.94	0.88	0.91	0.93	0.97	0.95	0.97	0.98	0.98	0.946	0.944
J48	0.91	0.88	0.89	0.93	0.93	0.93	0.95	0.98	0.97	0.933	0.930
RF	0.95	0.92	0.94	0.95	0.97	0.96	0.98	0.99	0.99	0.961	0.959
SVM	0.91	0.85	0.88	0.95	0.92	0.94	0.91	0.98	0.94	0.92	0.917

*P= Precision, R=Recall, F1= F1-Measure, Acc=Accuracy

5.1.3 Deep Learning Model Classification Results using All Features

5.1.3.1 Convolutional Neural Network

The implemented convolutional neural network model comprised of 6 hidden layers, one input layer and one output layer. Among hidden layers, first three are convolutional layers of filter size 3*3 with 32, 64 and 150 number of nodes respectively. Each of these three layers are followed by a ReLU activation function and responsible for feature mapping of input data. The fourth hidden layer is Max pooling layer of size 2 * 2, this layer is responsible for feature reduction. The fifth hidden layer is Flattening layer which is responsible for converting 2D feature set into a single array. The sixth hidden layer is Fully connected layer with 200 neurons just like simple neural networks. The number of layers and their parameters were fine tuned according to the effectiveness of model on given parameters. Figure 5.5 shows the architecture of CNN.

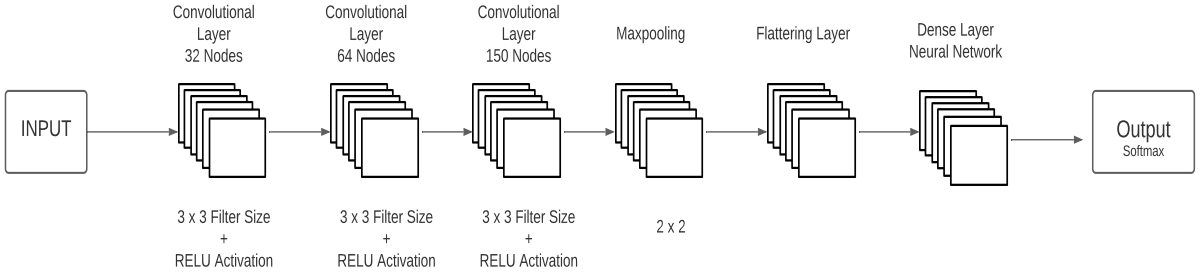


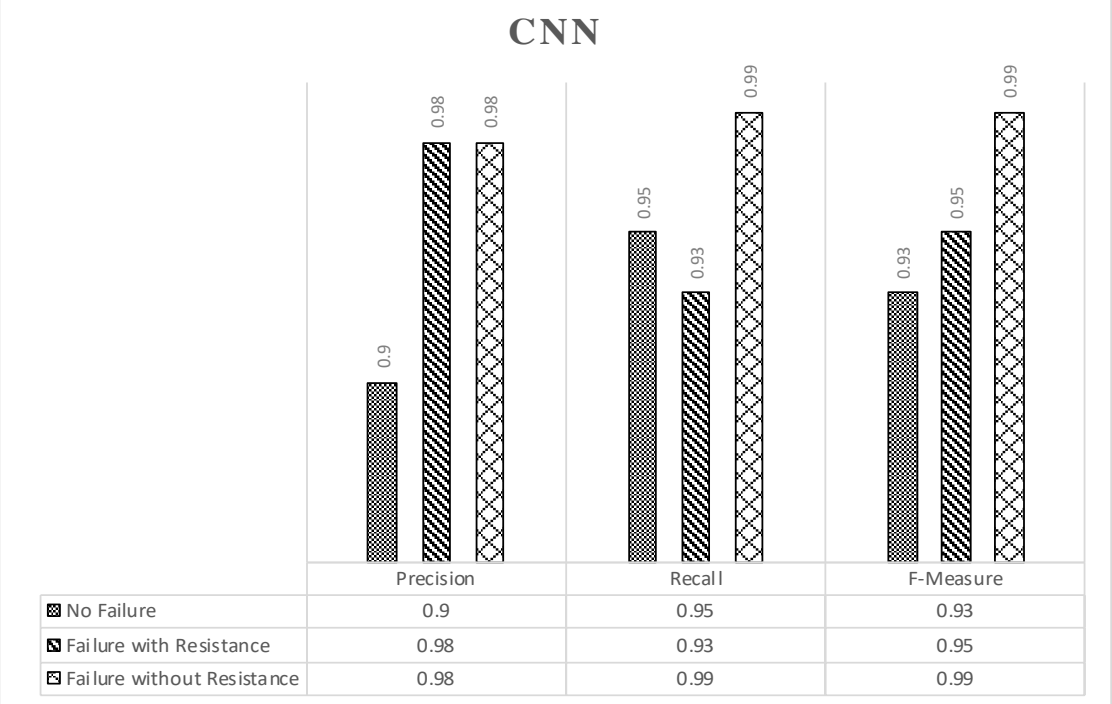
FIGURE 5.5: CNN architecture

Table 5.6 shows some of important parameters in CNN implementation:

TABLE 5.6: CNN parameters

Parameter	Value
Execution time	2 minutes
Epochs	20
Optimizer	Adam
Loss function	Categorical Cross entropy
Activation	Softmax and ReLU
Neurons	200
Validation data	15%
Weights	18, 30, 15
Seed	3
Learning Rate	0.001

Figure 5.6 shows the classification result of CNN model using all features set on different classes. Here CNN gives the f-Measure of 0.93 for no failure class, F-Measure of 0.95 for failure with resistance class and F-Measure of 0.99 for failure without resistance class.



	Precision	Recall	F-Measure
No Failure	0.9	0.95	0.93
Failure with Resistance	0.98	0.93	0.95
Failure without Resistance	0.98	0.99	0.99

FIGURE 5.6: CNN results for all classes with all features

Figure 5.7 shows the averages of precision, recall, f-measure and accuracy. Here CNN shows weighted F1 measure of 0.95 and accuracy of 0.96.

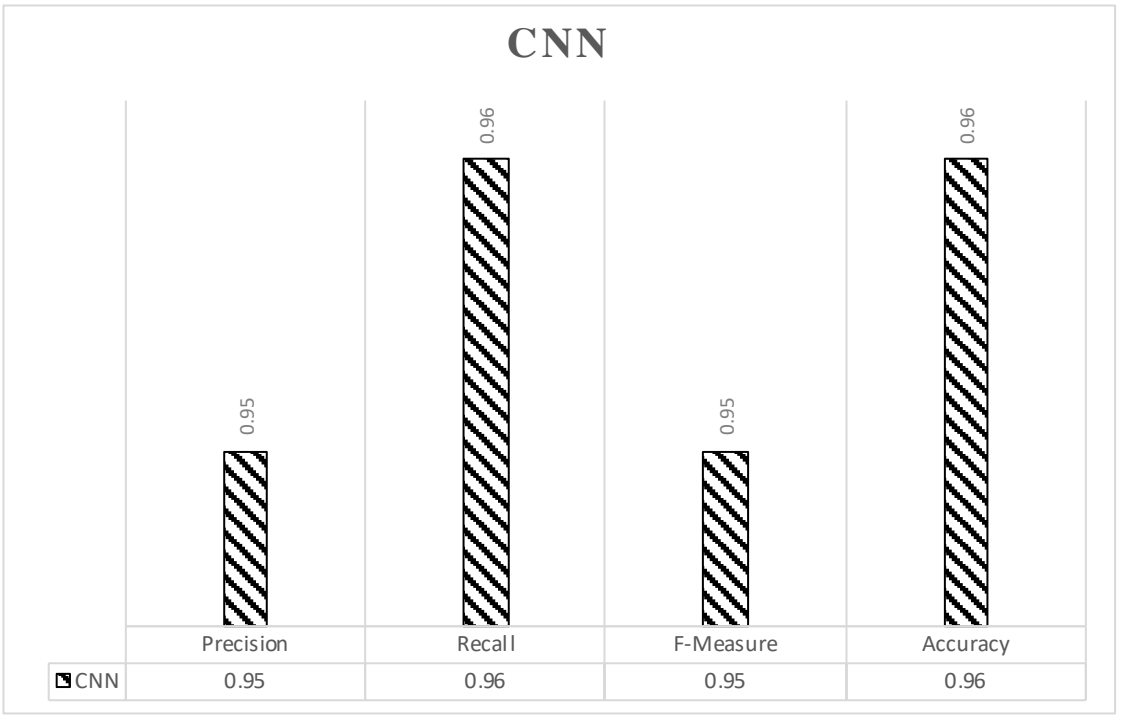


FIGURE 5.7: CNN results

5.1.3.2 AlexNet

For Alexnet default implementation has been used. The model consists of 11 hidden layers. First layer is convolutional layer of filter size 11 * 11 with 96 nodes, it is followed by ReLU activation function and second hidden layer of Max ppoling (3*3). Third hidden layer is also convolutional layer with filter size 5 *5 and 256 nodes followed by ReLU activation and max pooling layer (3 * 3). Fifth, sixth and seventh layers are convolutional layers of filter size 3 * 3 with 384, 384 and 256 nodes respectively. Next is again max pooling layer (3 * 3). Last three layers are fully connected layers with 4096, 4096 and 1000 neurons, each of last three layers is also followed by ReLU activation function. Figure 5.8 shows the architecture of AlexNet.

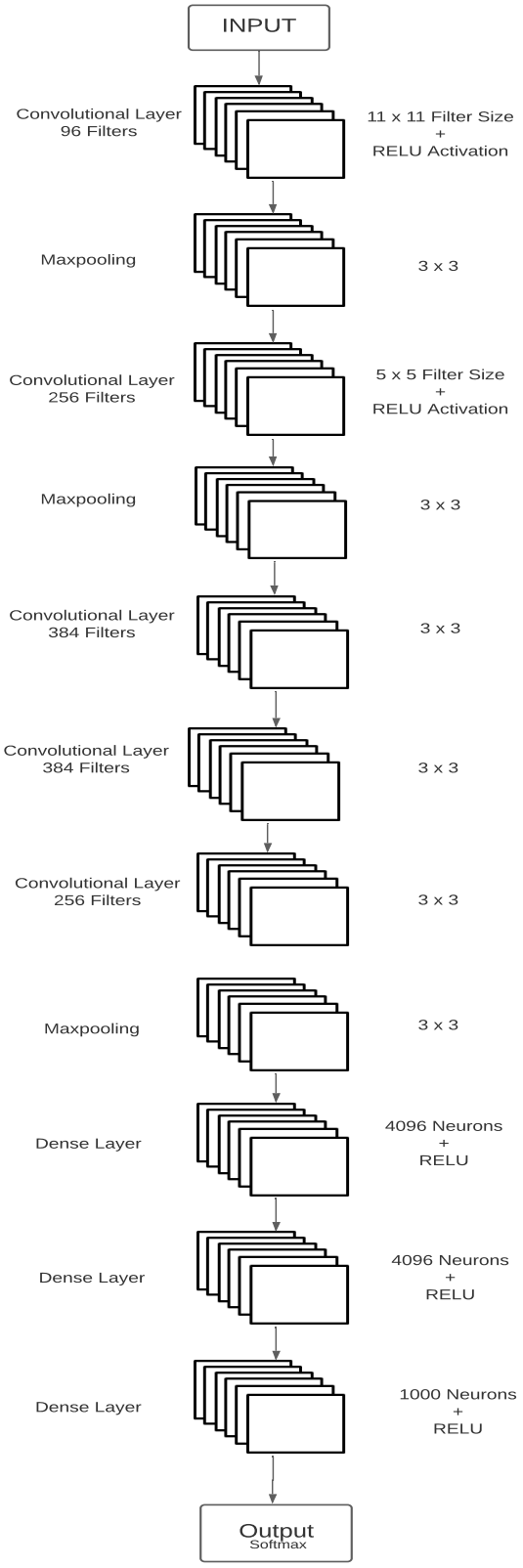


FIGURE 5.8: AlexNet architecture

Table 5.7 shows some of important parameters in AlexNet implementation:

TABLE 5.7: AlexNet parameters

Parameter	Value
Execution time	14.37 minutes
Epochs	20
Optimizer	Adam
Loss function	Categorical Cross entropy
Activation	Softmax and ReLU
Neurons	9192
Validation data	15%
Seed	3
Learning Rate	0.001

Figure 5.9 shows the classification result of AlexNet model using all features set on different classes. Here AlexNet gives the f-Measure of 0.89 for no failure class, F-Measure of 0.94 for failure with resistance class and F-Measure of 0.96 for failure without resistance class.

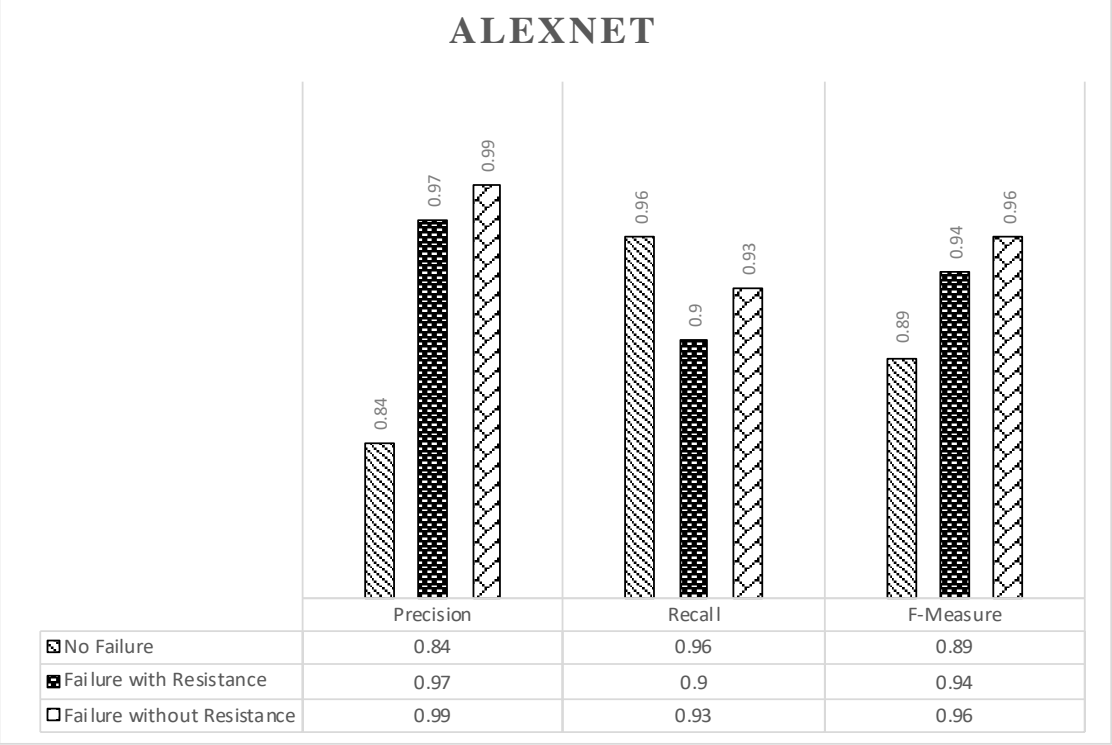


FIGURE 5.9: Alexnet results for all classes with all features

Figure 5.10 shows the weighted averages of precision, recall, f-measure and accuracy. Here AlexNet shows weighted F1 measure of 0.93 and accuracy of 0.93.

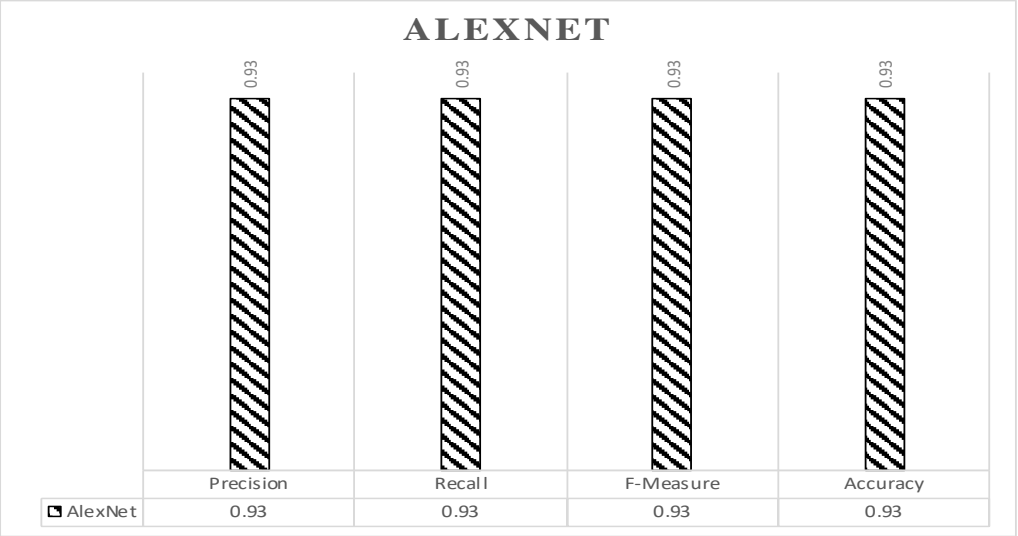


FIGURE 5.10: Alexnet results

5.2 Accuracy Comparison of ML Models

Figure 5.12 shows the accuracy under different experimental settings. With all features and class balancer, j48 shows highest accuracy of 0.865. With all features and SMOTE, random forest shows highest accuracy of 0.957. With reduced features and class balancer, random forest shows highest accuracy of 0.863. With reduced features and SMOTE, random forest shows highest accuracy of 0.961.

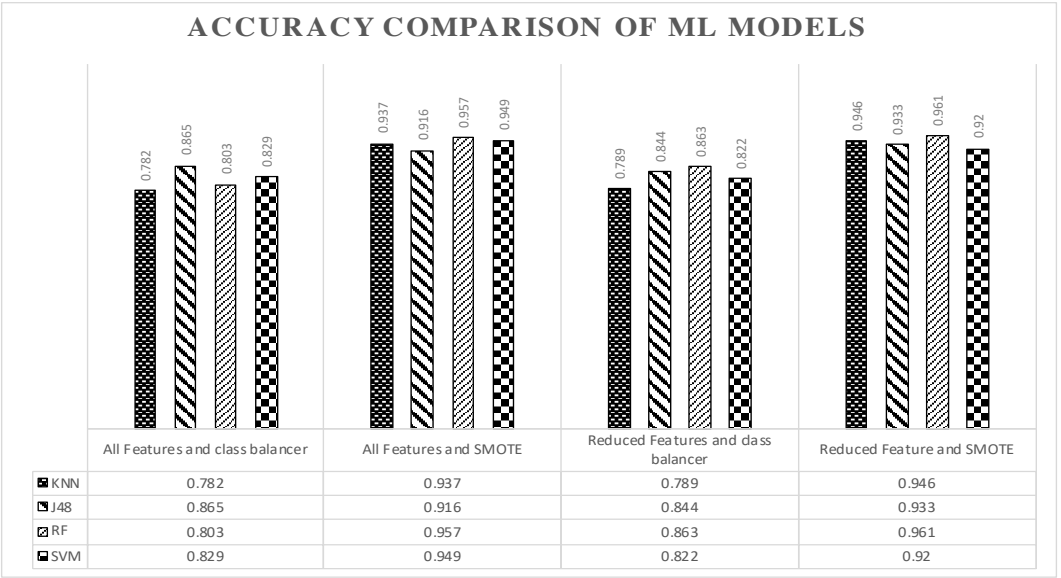


FIGURE 5.11: Accuracy comparison under different experimental settings

5.3 F-Measure Comparison of ML Models

Figure 5.12 shows the f-measure under different experimental settings. With all features and class balancer, j48 shows highest f-measure of 0.866. With all features and SMOTE, random forest shows highest f-measure of 0.956. With reduced features and class balancer, random forest shows highest f-measure of 0.866. With reduced features and SMOTE, random forest shows highest f-measure of 0.959.

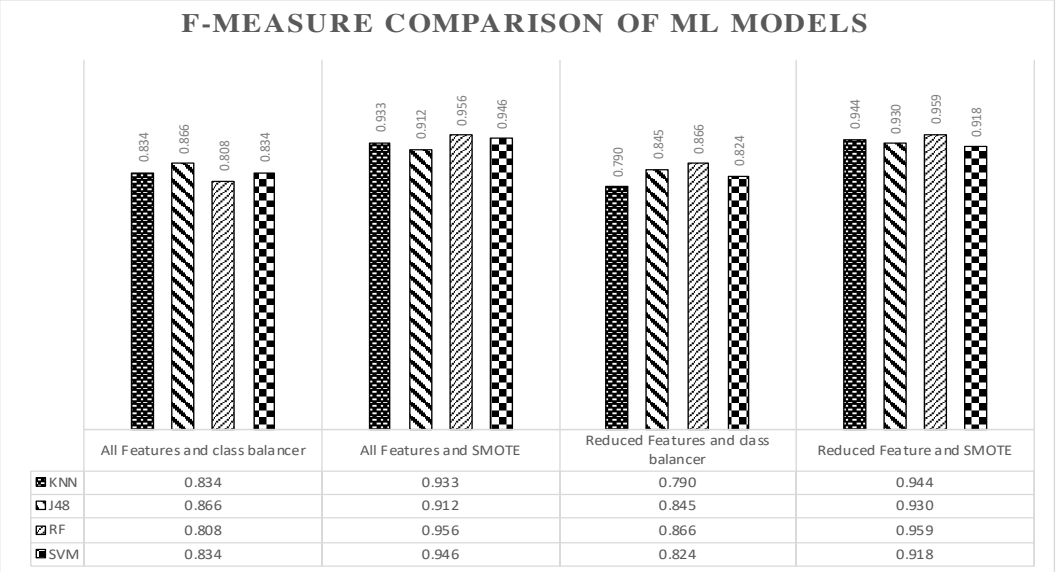


FIGURE 5.12: F-Measure comparison under different experimental settings

5.4 Comparison of Deep Learning Models

Figure 5.13 shows the accuracy and f-measure comparison of Deep Learning Models (CNN and AlexNet). With all features CNN shows accuracy of 0.96 and f-measure of 0.95. AlexNet shows accuracy of 0.93 and f-measure of 0.93.

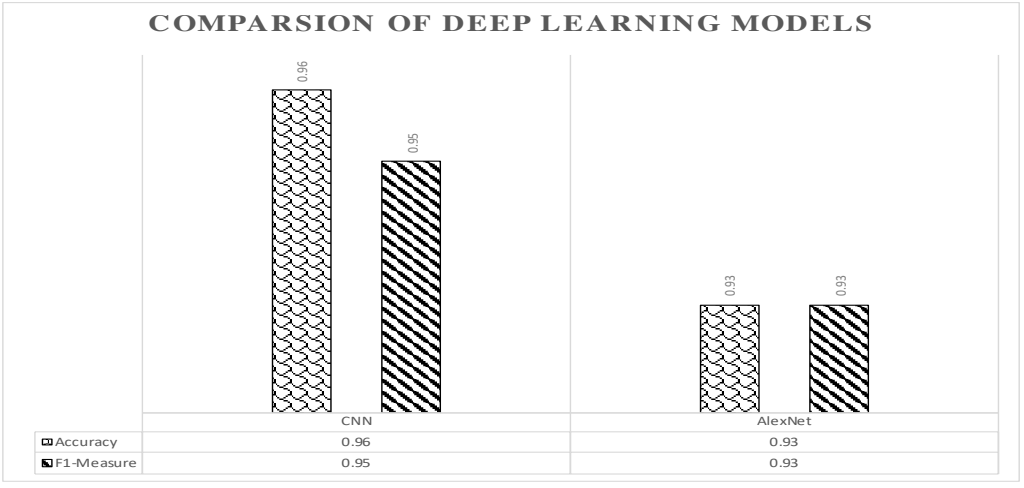
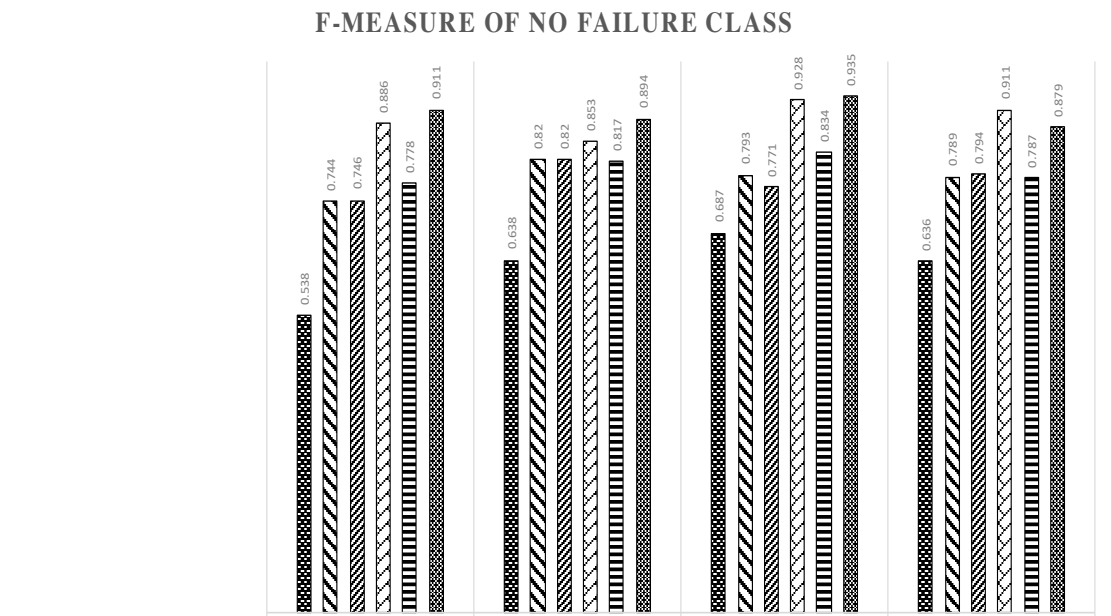


FIGURE 5.13: Comparison of deep learning models

5.5 Impact Analysis of Genomic and X-Ray Features

5.5.1 F-Measure of "No Failure"

Figure 5.14 shows that result of no failure class with respect to f-measure. It can be seen that by adding x-ray genomic features f-measure is improved. J48 shows the highest f-measure of 0.82 with all features and class balancer. Random forest shows the highest f-measure of 0.928 with all features and SMOTE. Random forest shows the highest f-measure of 0.83 with reduced features and class balancer. Random forest shows the highest F-measure of 0.935 with reduced features and SMOTE.



	KNN	J48	RF	SVM
Clinical and Demographic	0.538	0.638	0.687	0.636
CAD and Xray	0.744	0.82	0.793	0.789
CAD, Xray and Genomic (Class balancer)	0.746	0.82	0.771	0.794
CAD, Xray and Genomic (SMOTE)	0.886	0.853	0.928	0.911
Reduced Features and class balancer	0.778	0.817	0.834	0.787
Reduced Feature and SMOTE	0.911	0.894	0.935	0.879

FIGURE 5.14: F-Measure of no failure class by using different features

5.5.2 F-Measure of "Failure with Resistance"

Figure 5.15 shows that result of failure with resistance class with respect to F-measure. It can be seen that by adding other features i.e. X-ray and genomic features, f-measure is improved for this class as well. J48 shows the highest f-measure of 0.871 with all features and class balancer. Random forest shows the highest F-measure of 0.955 with all features and SMOTE. Random forest shows the highest F-measure of 0.877 with reduced features and class balancer. Random forest shows the highest F-measure of 0.958 with reduced features and SMOTE.

	KNN	J48	RF	SVM
Clinical and Demographic	0.468	0.459	0.717	0.744
CAD and Xray	0.775	0.783	0.821	0.815
CAD, Xray and Genomic (Class balancer)	0.812	0.871	0.832	0.858
CAD, Xray and Genomic (SMOTE)	0.94	0.914	0.955	0.946
Reduced Features and class balancer	0.807	0.862	0.877	0.847
Reduced Feature and SMOTE	0.945	0.931	0.958	0.935

FIGURE 5.15: F-Measure of failure with resistance class by using different features

5.5.3 F-Measure of "Failure without Resistance"

Figure 5.16 shows that result of failure without resistance class with respect to f-measure. It can be seen that by adding other features i.e. x-ray and genomic features, F-measure is improved for this class as well. J48 shows the highest F-measure of 0.908 with all features and class balancer. Random forest shows the

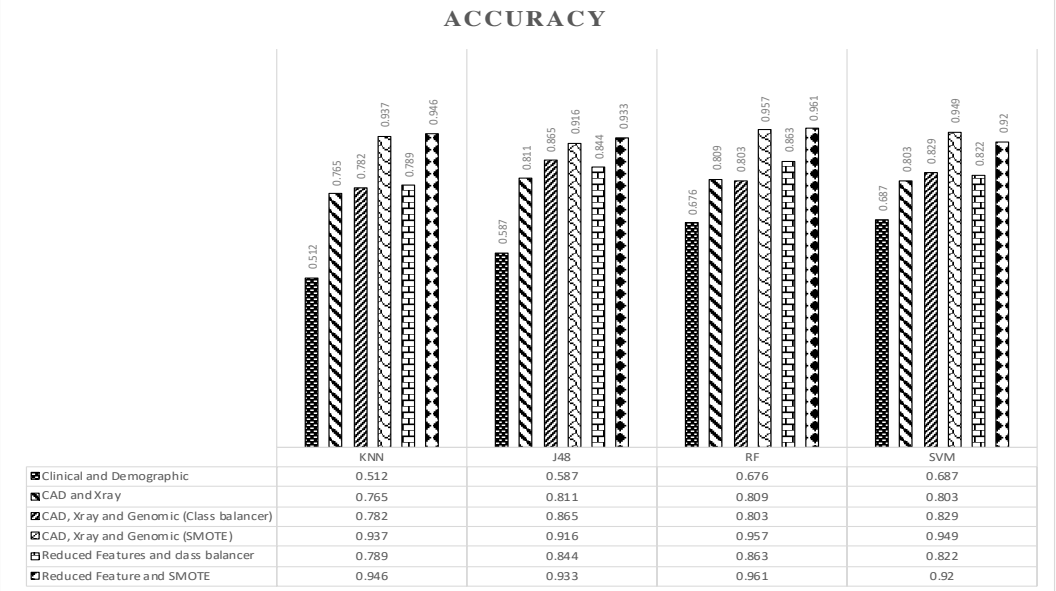
highest F-measure of 0.985 with all features and SMOTE. Random forest shows the highest F-measure of 0.886 with reduced features and class balancer. Random forest shows the highest F-measure of 0.985 with reduced features and SMOTE.

	KNN	J48	RF	SVM
Clinical and Demographic	0.397	0.636	0.612	0.696
CAD and Xray	0.79	0.848	0.82	0.813
CAD, Xray and Genomic (Class balancer)	0.806	0.908	0.82	0.85
CAD, Xray and Genomic (SMOTE)	0.974	0.968	0.985	0.98
Reduced Features and class balancer	0.786	0.857	0.886	0.838
Reduced Feature and SMOTE	0.977	0.966	0.985	0.939

FIGURE 5.16: F-Measure of failure without resistance class by using different features

5.5.4 Accuracy using Different Features

Figure 5.17 shows that result of all features with respect to accuracy. It can be seen that by adding other features i.e. x-ray and genomic features, Accuracy is improved. J48 shows the highest Accuracy of 0.865 on all feature set with class balancer. Random forest shows the highest accuracy of 0.957 with all features and SMOTE. Random forest shows the highest accuracy of 0.863 with reduced features and class balancer. Random forest shows the highest accuracy of 0.961 with reduced features and SMOTE.

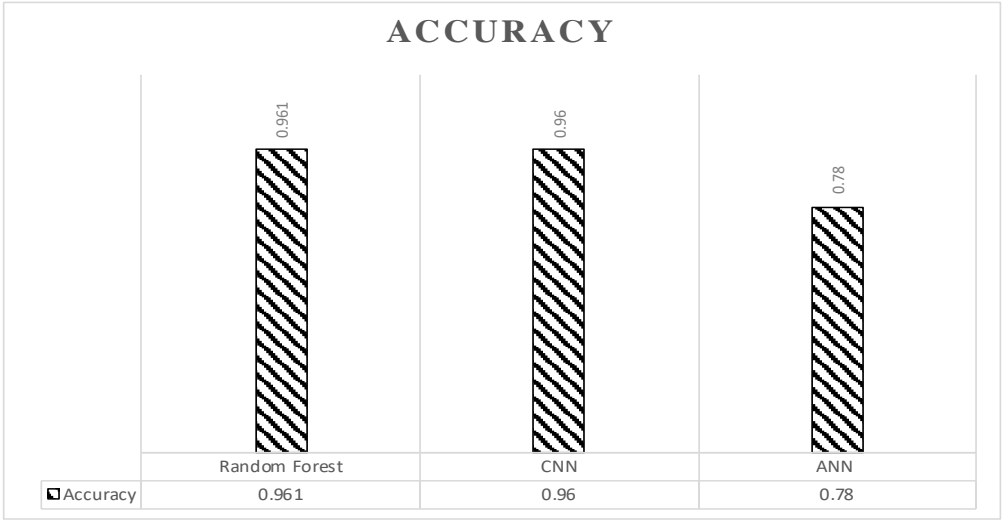


	KNN	J48	RF	SVM
Clinical and Demographic	0.512	0.587	0.676	0.687
CAD and Xray	0.765	0.811	0.809	0.803
CAD, Xray and Genomic (Class balancer)	0.782	0.865	0.803	0.829
CAD, Xray and Genomic (SMOTE)	0.937	0.916	0.957	0.949
Reduced Features and class balancer	0.789	0.844	0.863	0.822
Reduced Feature and SMOTE	0.946	0.933	0.961	0.92

FIGURE 5.17: Accuracy comparison of different ML models by using different features

5.6 Comparison with Existing Work

Figure 5.18 shows accuracy comparison of presented approach with the approach used in [24]. Highest accuracy of base paper was 0.78. Highest accuracy of 0.961 has been achieved using machine learning model and deep learning model shows accuracy of 0.96. Both ML model and Deep Leaning approach shows better result than the base paper. Deep learning model (CNN) require complete set of features which increases the computation of prediction whereas if you have selected feature set then machine learning model (Random Forest) is better than deep learning model (CNN).



	Random Forest	CNN	ANN
Accuracy	0.961	0.96	0.78

FIGURE 5.18: Accuracy comparison with [24]

5.7 Discussion

Discovering general feature set for different countries which have vary in culture, literacy rate, health, death rate etc. is a very difficult task. The purpose of this research is to discover such feature set by utilizing different Machine Learning and Deep Learning Models. To achieve the objective, dataset of 7 different counties have been collected which are Azerbaijan, Belarus, Kazakhstan, Georgia, Moldova, Ukraine and Romania. Dataset is collected from TB Portal website which is updating timely. This research used dataset until May 2021. Dataset consist 151 features of approximately 2441 patients. Data include 24 Demographic and Clinical Features, 55 X-Ray and CT features, 71 Genomic and Sequenced Data Features.

Preprocessing is performed on Raw Data to prepare it for models. Further it was observed that there exists class imbalance problem due to high percentage of no failure patients. Two techniques which are Class Balancer and SMOTE are being used to tackle this problem. Feature set might contain irrelevant features affecting the prediction accuracy; therefore, Information Gain and Ranker have been used to eliminate irrelevant features and obtain more relevant feature set. The reduced feature set comprise of 27 attributes (15 Clinical and Demographic, 4 X-ray and 7 Genomic). Machine Learning Model J48, KNN, RF and SVM and Deep learning models CNN and AlexNet are used for classification. Six different experiments are performed and evaluated for better prediction.

In experiment 1, all features along with class balancer are used for training by machine model which provide the highest accuracy of 0.86. In experiment 2, all features along with SMOTE are used for training by machine model which provide the highest accuracy of 0.95. In experiment 3, reduced features along with class balancer are used for training by machine model which provide the highest accuracy of 0.86. In experiment 4, reduced features along with SMOTE are used for training by machine model which provide the highest accuracy of 0.961. In experiment 5, all features are provided to Deep Learning model (CNN) which provide the highest accuracy of 0.96. In experiment 6, all features are provided

to Deep Learning model (AlexNet) which provide the highest accuracy of 0.93. Previous studies achieved the highest accuracy of 0.78 by ANN. So, proposed study provides the better result than the prior studies. Proposed study also provides the generalized feature set.

Experiments are also performed on different types of attributes to check the impact of Genomic and X-Ray features. With only Clinical and Demographic feature set, SVM shows the highest accuracy of 0.68. With X-Ray feature along with Clinical and Demographic, J48 shows the highest accuracy of 0.81. With all features set, J48 shows the highest accuracy of 0.86 using Class Balancer Technique. With all features set, RF shows the highest accuracy of 0.957 using SMOTE Technique. With reduced features set, RF shows the highest accuracy of 0.863 using Class Balancer Technique. With reduced features set, RF shows the highest accuracy of 0.961 using SMOTE Technique. With all features Deep Learning model CNN shows the highest accuracy of 0.96 and AlexNet shows the accuracy of 0.93.

Summary

This chapter explains different experiments which are conducted and respective results are compared. The six experiments which are conducted are ML classification results with all features using class balancer, ML classification results with all features using SMOTE, ML classification results with reduced features using class balancer, ML classification results with reduced features using SMOTE, Deep Learning Model (CNN) classification results using all features and Deep Learning Model (AlexNet) classification results using all features. With reduced features and SMOTE, Random Forest shows highest accuracy of 0.961 and CNN shows accuracy of 0.96 with all features.

Chapter 6

Conclusion and Future Work

6.1 Conclusion

In this study new features of x-ray and genomic are used for prediction of tuberculosis treatment failure along with clinical and demographic features. Machine learning and Deep learning models are applied in this study. The experiment's results have shown that there is a vital impact of x-ray and genomic features in prediction of tuberculosis treatment failure.

In proposed work, it is concluded that the one of the main reasons behind TB treatment failure is Drug Resistance, therefore using only clinical and demographic feature can provide only limited prediction accuracy. One must use genomic and X-ray features which are related to Drug resistance. Machine learning models are performing well and have the highest accuracy in prediction of TB treatment failure. J48 shows accuracy of 0.865 by using all features with class balancer. Random forest shows accuracy of 0.957 by using all features with SMOTE. Random forest shows accuracy of 0.863 by using reduced features with class balancer. Random forest shows accuracy of 0.961 by using reduced features with SMOTE. Machine Learning approaches required pre-processing steps like class balancing, Feature Selection etc. to accomplish best results. On the other hand, Deep Learning model require no such effort and is still providing handsome results. CNN shows the

accuracy of 0.96 by using all features. This study also provides the generalized feature set which are more relevant to treatment failure.

6.2 Future Work

In future we have plan to investigate and identify demographic specific reduced features set to target the prediction of this multi classes problem (No Failure, Failure with Resistance and Failure without Resistance). Tuberculosis Drug Resistance exist in different forms due to mutation of MycoBacterium such as Mono, Poly, MDR, XDR and RR. In future we can explore these types of resistance as well by predicting the type of resistance in TB patient so that the treatment can be adjusted accordingly.

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