Review

ARTIFICIAL INTELLIGENT-POWERED DETECTION OF TUBERCULOSIS

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Abstract: Tuberculosis (TB) disease still remain a major global threat due to the growing number of drug-resistant species and global warming. Despite the fact that there are new molecular diagnostic approaches, however, majority of developing countries and remote clinics depends on conventional approaches such as Tuberculin test, microscopic examinations and radiographic imaging (Chest X-ray). These techniques are hindered by several challenges which can lead to miss-diagnosis especially when interpreting large number of sample cases. Thus, in order to reduce workload and prevent miss-diagnosis, scientists incorporated computer-aided technology for detection of medical images known as Computer aided Detection (CADe) or Diagnosis (CADx). The use of AI-powered techniques has shown to improve accuracy, sensitivity, specificity. In this review, we discussed about the epidemiology, pathology, diagnosis and treatment of tuberculosis. The review also provides background information on Artificial Intelligence (AI), Machine Learning (ML), Deep Learning (DL), Transfer Learning (TL) and their applications in detection of tuberculosis from both microscopic slide images and X-ray images. The review also proposed an IoT/AI powered system which allows transfer of results obtained from DL models with end users through internet networks. The concept of futuristic diagnosis, limitations of current techniques and open research issues are also discussed.

Keywords: Tuberculosis, Artificial Intelligence, Machine Learning, Deep Learning, Transfer Learning, Computer-aided Diagnosis

1. Introduction

The world is constantly facing emergence and reemergence of infectious diseases which causes significance burden to the lives of human and non-human primates. Infectious diseases can be subdivided into different categories based on the causative pathogen which include bacteria, viral, fungi and parasites. The cycle of infectious diseases includes host, pathogen and in certain cases intermediate host or vector. Some of the factors that determines the suitable habitat/ecological niche for every vector host depends on environmental factors such as temperature and humidity [1].

Bacteria are microscopic organisms made up of single cell and are ubiquitous in nature. They stored their genetic material in the form of double-stranded DNA while some species contain additional small cellular plasmid. They can be classified as either non-pathogenic such as microbiome which are pound in the gut and intestine or pathogenic. Despite the fact that most bacteria are non-pathogenic, however, pathogenic bacteria are very harmful and can cause diseases ranging from whooping coup, skin diseases, respiratory diseases, ear infection, urinary tract diseases (UTI). Some of the examples of bacterial diseases include tuberculosis, bacterial pneumonia, meningitis, cholera, anthrax, gonorrhea, syphilis etc. [2-3].

Unlike bacteria that store their genetic content in the form of DNA and majority are non-pathogenic, viruses stored their genetic content in the form of RNA and are mostly pathogenic in nature. Viruses affect both human and non-human primates and surprisingly, viruses also affect bacteria (e.g., bacteriophage). The pathogenicity of viruses revolves around hijacking host's nucleic acid replication system which supplies all the necessary machinery and enzymes suitable for viral replication. An example of viral diseases includes the current COVID-19, HIV/AIDs, Ebola disease, Dengue fever, yellow fever, common cold, Chickenpox, smallpox, measles, influenza, herpes etc. [4-6].

Over the past century, scientists from all over the world have been trying to develop more rapid, precise, accurate and efficient diagnostic approaches for detection of infectious disease. Some of these approaches revolves around microbiological identification, characterization and molecular techniques. Considering the fact that majority of pathogenic diseases are caused by microorganisms, medical technologies rely solely on microbiological identification, characterization, morphology etc. These techniques are useful for identifying pathogenic diseases based on staining techniques, antibiotic susceptibility profiling, isoenzyme profiling as well as chromatographic analysis of cellular fatty acids [7-8].

The low sensitivity and specificity of conventional microbiological approaches have led scientists to developed molecular techniques which harness the specificity or molecular interactions of enzyme and substrate, antigen and antibody, template and target nucleic acid, whole cell and receptor. In the last few years, antigen-antibody and nucleic acid techniques such as plasmid profiling, Polymerase Chain Reaction (PCR) (e.g., RT-PCR) and mostly CRISPR/Cas-based biosensing have emerged as the most efficient molecular approaches for the detection of infectious diseases [9-11].

Despite the specificity of molecular approaches, they are still hindered by several challenges such as the requirements of sophisticated equipment, toxic chemicals or laboratory reagents, skillful and trained pathologists, longer processing time, false positive results, lack of point-of-care testing. Thus, these challenges have opened the gateway for incorporating other technologies for the development of ideal or an improved diagnostic approach [12-13].

Advancement in science and technology has given birth to other fields such as nanotechnology, electronics, computer sciences, AI, Internet of things (IoT) etc. Integration of one or more of these technologies have shown to improve desired characteristics [14]. CAD is born out of the wedlock between medical data (imaging, signals, numerical) and computer sciences [15]. The development of AI-driven models in the last decades has increase the efficiency of computer devices in terms of classifying objects images and predicting outcomes. The integration of these models into medical field have shown to reduce workload, error or miss-diagnosis and simultaneously increase accuracy and efficiency [16]. Abbreviations used in this study are presented in table 1.

Table 1. Abbreviations

Abbreviations	Full meaning
AI	Artificial Intelligence
ANNs	Artificial Neural Networks
AUC	Area Under the Curve
CADe	Computer-Aided Detection
CADx	Computer-Aided Diagnosis
CNNs	Convolutional Neural Networks
COVID-19	Coronavirus Disease 2019
CT	Computed Tomography
CXR	Chest X-ray
DCNNs	Deep CNNs
DL	Deep Learning
DNA	Deoxyribonucleic Acid

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ENet	Efficient Net
FRCNN	Faster Region-based CNN
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
ILSVRC	ImageNet Large-Scale Visual Recognition Challenge
IoT	Internet of Things
MBTB	Mycobacterium Tuberculosis
ML	Machine Learning
MRI	Magnetic Resonance Imaging
PCA	Principal Components Analysis
PCR	Polymerase Chain Reaction
PET	Position Emission Computed Tomography
PPD	Purified Protein Derivative
ReLu	Rectified Linear Unit
RFID	Radio Frequency Identification
ROIs	Regions of Interests
RT-PCR	Reverse Transcripts PCR
SARSA	State-action-reward-state-action
SMOTE	Synthetic Minority Oversampling Technique
SPECT	Spectro Emission Computed Tomography
SVM	Support Vector Machine
TB	Tuberculosis
TL	Transfer Learning
TST	Tuberculin Skin Test
UTI	Urinary Tract Diseases
ZN	Ziehl-Nelsen

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1.1 Comparison with Similar Studies

Despite the fact that there are several research articles on molecular, microscopic and automated detection of TB. However, few studies attempted to provide review on the pathology, epidemiology, diagnosis, treatments of TB as well as the integration of AI-driven technology for the screening of the disease. In this subsection, we overview these surveys and highlights how it contrasts with our own review as shown in table 1.

The review provided by Kulkarni and Jha [17] provide an overview on TB, detection of TB using radiographic images and CAD of TB based on DL. Despite the wide range of topics covered, the study does not exclusively cover microscopic diagnosis, propose an IoT/AI-based powered system and open research issue. Similarly, Harris et al. [18] focus on automated detection of TB using radiographic images. The use of microscopic evaluation and IoT-based platform are out of the review scope. Another review that focuses on detection of TB from radiographic images was provided by Cao et al. [19]. The study only focuses on the application of CAD technology on detection of TB. The review provided by Chassagnon et al. [20] cover broad subtopics under thoracic imaging which include TB and pneumonia. The study highlighted on radiographic imaging of TB, the use of AI-driven model for the classification of the disease. However, the study does not cover microscopic imaging as well as the futuristic IoT-based diagnostic approach for detection of TB.

The review provided by Meraj et al. [21] shared a lot of similarities with our report. The review also discussed about TB, types, conventional diagnosis, AI-driven models. However, the study does not extensively cover radiographic images, propose IoT/AI-based system and open research issue. Another review that resembles our report was provided by Dande and Samant [22]. The study covers TB, diagnosis (molecular, microscopic and radiographic) as well as automated detection of TB using ML models and future scope. The only distinction between this report and our study is that our report presented futuristic automated and smart diagnostic approach by merging microscopic slide images, radiographic images with both DL and IoT systems.

Table 1. Comparison with similar studies

References	TB pathology	Molecular Diagnostic	Medical Imaging	AI, ML, DL and TL	Proposed System	Open Research Issue
[17]	✓	-	✓	✓	-	-
[18]	✓	-	✓	✓	-	-
[19]	✓	-	✓	✓	-	-
[20]	✓	-	✓	✓	-	✓
[21]	✓	-	✓	✓	-	-
[22]	✓	✓	✓	✓	-	-
Our Report	✓	✓	✓	✓	✓	✓

2. Materials and Methods

The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

2. Tuberculosis

TB has been major global burden in terms of lives, economic and social activities of humankind for the past few years. Despite the fact that there were several pandemics that consume millions of lives such as plague and smallpox, however, majority of these diseases are short-live. Unlike TB which continue to inflict human population in terms of mortality and morbidity. Several drugs such as antibiotics have been developed by different pharmaceutical companies to target the bacteria, yet the disease continue to cause havoc due to development of antibiotic resistance [23].

2.1 History and Epidemiology

Despite the fact that the pathology of TB has become known in the 19th century, however, TB is regarded as one of the oldest diseases dating back to ancient times and civilizations. Ancient documents and literature have made references of a disease similar to TB in terms of transmission and symptoms. One of the earliest references to the disease was mentioned in the Sanskrit language. The description of similar diseases to TB has also been documented in Arabic and Chinese literatures. The Vedas an ancient Indian scripture also mentioned the disease as wasting disease (Known as Yakshma). Moreover, the ancient English literature describe the disease as "Consumption" which is derived from Latin word known as "Consumer". The current name TB is also associated with Latin word known as "Tubercula" which means "Small lump" [23, 25].

Trailing only after HIV, TB is regarded as the second deadliest disease which account for an estimated deaths of over 1.4 million in 2019 prior to COVID-19 pandemic. More than 10 million people developed the disease which include 1.2 million children, 3.2 million women and 5.6 million men. The disease is predominant in many underdeveloped and developing countries which include Bangladesh, India, Indonesia, Nigeria, Pakistan, Philippines, South Africa and also China [24].

TB is an airborne disease caused by bacterium known as Mycobacterium tuberculosis (MBTB). MBTB are rod in shape, slender ranging from 2 to 4 micrometers in shape. The bacteria are strictly aerobic in nature which means they survive in an environment rich with oxygen. They have a waxy cell wall due to the presence of mycolic acid which also contribute to their acid-fast feature. This attribute makes the bacteria retain on to a stain or specific dye such as the Ziehl-Nelson (ZN) stain which makes the bacteria look red in color. Moreover, the waxy cell wall also contributes to their ability to repelled weak disinfectants [25].

2.2 Transmission

Like majority of bacteria that infected the lungs, MBTB can also be transmitted as a result of inhaling the bacteria expelled by infected person to another person via coughing, sneezing, speaking, spitting etc. [26]. As the droplets moves to the lungs, the body employed different defensive mechanism to destroy the bacteria. One of these defensive mechanisms is the toxicity of the air in the upper airways which drives the bacteria against the mucus. Secondly, if the bacteria escape the airways, the macrophages in the lungs engulfed and destroy the bacteria due to the presence of hydrolytic enzymes. However, MBTB is equipped with defensive mechanism by secreting proteins that can inhibit the action of the enzymes which lead to pulmonary TB making the patient symptomatic as shown in Figure 1 [26-27].

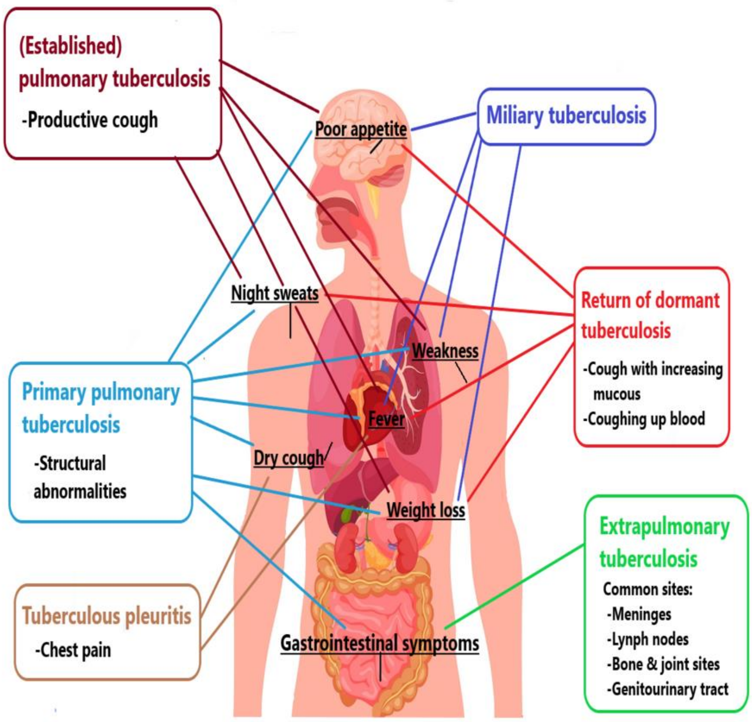

Figure 1. Types of TB

In order to prevent the bacteria from proliferating, the body initiate the third defense mechanism using immune cells which lead to the formation of Granuloma. When the tissue inside the granuloma dies through a process known as "Caseous Necrosis," the area is described as Ghon complex or focus. Additionally, the dead-tissue inside the granuloma undergoes a process known as "Fibrosis or calcification" which leads to the formation of a scar tissue which can be detected using Xray. Despite this defensive mechanism, the bacteria can escape into close by lymph leading to caseation. In some cases, the bacilli can remain in a latent state (i.e., dormant) and can be triggered when the immune system is weakened due to infections (such as HIV/AIDS) as well as ageing [27-28].

MBTB can also spread to the upper lobes of the lungs which contain high concentration of oxygen. Systematic miliary TB is termed as a form of TB which result from spread of the bacteria into other tissues and organs. The presence of MBTB in these organs can lead to diseases such as sterile pyuria of the kidneys, hepatitis in the liver meningitis in the brain etc. [29]. TB can be classified as either pulmonary (which affect the lungs) and extrapulmonary which affects other organs such as spine, kidneys and brain. TB can also be classified as either latent (dormant) or active (which is contagious and can be transmitted from infected person to healthy person). The disease can cause organs dysfunction and if not treated can lead to the deaths [30]. Some of the symptoms of TB include fever, cough, fatigue, night sweet, chills, loss of appetite, chest pain, weight loss etc. as shown in Figure 2 [31].

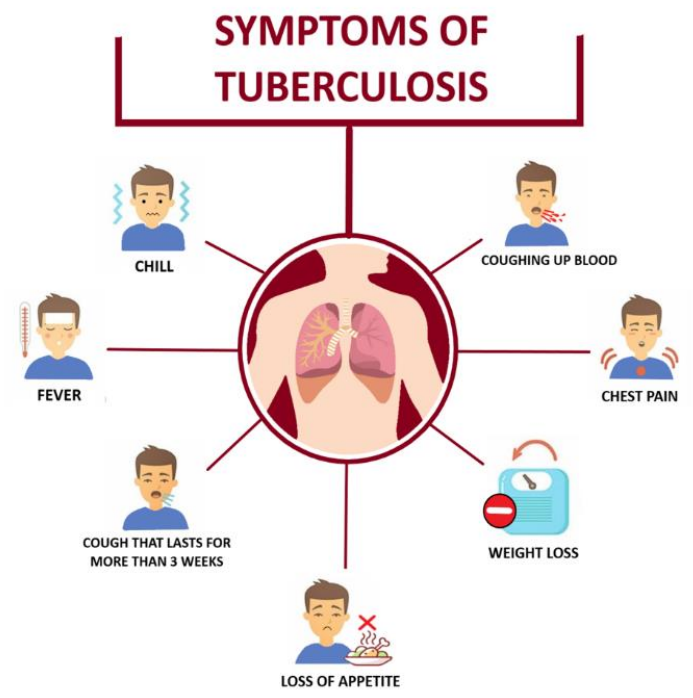

Figure 2. Symptoms of TB

2.3 Diagnosis of tuberculosis

There are several approaches developed by scientists for the diagnosis of TB. However, the 3 most common techniques include culture test, acid-fast staining microscopy and X-ray imaging. Other approaches include Purified Protein Derivative (PPD), Tuberculin Skin Test (TST), Interferon γ-release assay, GeneXpert etc. One of the most popular and most adopted approach utilized by medical experts globally is the microscopic sputum smear evaluation using microscope due to its simplicity, speed and affordability [25, 32].

Microscopic Evaluation

Since the invention of microscope in the 16th century, the device has been applied in medical field for diagnosis of disease and biology for study of microorganisms and cellular component. Technological advancement in the field of microscope has led to the invention of high magnified digital and electronic microscope that are currently in use for diagnosis of number of conditions such as TB, malaria, pneumonia etc [33]. Microscopic examinations and evaluations are the leading screening approaches use in remote areas, low-resource clinics, high disease burden areas due to their versatility, simplicity and affordability. Consequently, the evaluation of microscopic slide images can be time consuming and tedious for Microbiologists and as a result can leads to miss-diagnosis [11, 34].

Culture test: In order to conduct culture test for the detection of TB, medical expert collect sputum samples from suspected patients. The sample is then cultured in a biosafety hood or sterilize environment. The culture is left to grow under regular observation in a negative pressure room for 4-8 weeks. In order to prevent spread of the pathogen and transmission to medical personnel, safety measures must be observed such as wearing isolation clothes [35].

Acid Fast Staining: Acid fast staining technique is one of the most widely adopted approach for the detection of TB. A common example of acid-fast staining is the ZN stain. This technique takes advantage of the presence of mycolic acid which is present in the bacterial wall and contribute to the bacterial resistant to decolorization by acid-alcohols. Subsequent visualization of the bacteria treated with ZN stain under microscope exhibit red/pink rods/bacilli against a blue background [36]. The incidence of false negative results in patients suffering from active pulmonary TB is apparent using sputum culture test which is regarded as the gold standard technique for detection of TB [37].

X-ray imaging: Discrimination between active and latent TB is crucial for diagnosis. By using X-ray imaging, scientist can detect active TB as a result of the presence of consolidation and cavitation lesions in the patient's lungs while latent TB is characterized by stable fibronodular changes (I.e., scaring and nodular opacification [17].

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2.4 Treatment of TB

Medical experts prescribed different treatment approaches depending on the severity of the disease as well as stage of diagnosis. The use of antibiotics and other drugs are common for the treatment of laten TB. An example of drugs commonly use is Isoniazid which is prescribed to be taken for a prolong period of time. For treatment against TB, the first stage involves isolation of patient due to the contagiousness of the bacteria and the use of combinations of several antibiotics. One of the challenges facing the treatment and control of TB is that the bacteria can become resistant to antibiotics. Thus, physician prescribed combination of broad drugs [26, 29].

3. Computer-aided Diagnosis

The concept of Computer Aided Detection (CADe) or Computed Aided Diagnosis (CADx) referred to the application of computer machineries (such as software, applications and hardware) to assists medical expert in diagnosis, screening and in decision making [15]. Medical experts employ medical data such as conventional imaging (CT scans, X-ray, MRI, ultrasound, microscopic etc.), nuclear imaging (Position Emission Tomography and Spectro Emission Computed Tomography), signals (electrocardiogram, electroencephalogram), numerical data such as concentration and volume to evaluate information such as abnormality, features, grades etc for appropriate diagnosis. In medical field, interpretation of these diagnosis using medical images is very critical due to the probability of miss-diagnosis which can be detrimental [38-39].

The concept of CAD system revolves around the use of several techniques such as computer vision, medical image processing, AI etc. The main objective of CADe or CADx system is to screen or detect abnormality in medical data such as identification of potential Regions of Interests (ROIs) or providing quantified image metrics to compute probabilities of different diagnoses [40]. CAD has been adopted in medical field for the screening and detection of several infectious and pathological diseases which include pneumonia (viral and bacterial), TB, COVID-19, skin diseases and lesions, cancer or tumor (breast, colon, lung, prostate etc.), diabetic retinopathy from medical images. CAD systems has also been applied for diagnosis of brain diseases such as Alzheimer's disease and coronary artery disease [39-40].

Despite the fact that the first application of CAD system can be dated back to the 1990s, however, the technology is yet to reach its full potential. Thus, several progress and advancement had been made in the last 2 decades. This advancement can be attributed to the development of DL models as subsidiaries of ML and AI. The 2 most common DL approaches applied in medical screening and detection include Convolutional Neural Networks (CNNs) and Artificial Neural Networks (ANNs). There are several existing AI-driven models that have shown to outperformed medical experts in terms of classification of medical data and interpretation [41]. Majority of the images acquired from medical tools have low contrast, quality and resolution. Thus, in order to enhance these limitations, scientists adopt several image processing techniques such as filtering, decreasing background artefacts, noise removal, levelling etc.

3.1 Artificial Intelligence (AI)

The concept of AI, ML, DL and TL have been trending over the past years due to their wide application in almost every discipline. The concept of AI revolves around the use of programs to enable computer perform some certain functions. AI is a sub branch of computer science concerned with building smart machines that have the ability to perform several tasks that typically require human intelligence. The concept of AI is inspired by the cognitive function of the human mind in terms of learning, problem solving and decision making. Thus, AI can be a program that dictate how machine behave in a specific way. AI has several applications such as computer vision, expert system, speech recognition, natural language processing etc. The field of AI is transforming communication, transportation, diagnosis, weather forecast and other facet of human lives. An example of AI applications includes Alexa and Siri, self-driving cars, robots etc. [42-43].

3.2 Machine Learning (ML)

The concept of ML can be dated back to 1960s where traditional ML approaches were developed. The application of AI can be seen in weather forecasting, internet search engines. ML use algorithm whose performance improve as they are exposed to large amount of data. Thus, if ML is a vehicle, then data, is the fuel. ML revolves around the use of algorithms to perform various tasks such as classification, regression, clustering etc. ML are categorized into supervised ML, Unsupervised ML and Reinforcement ML [44].

Supervised ML is defined as a sub-branch of ML that employ labelled datasets which are train by applying algorithms in order to predicts or classify data accurately. In order to conduct supervised ML tasks, scientists classified labelled data into training, testing and

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validation sets. The models are trained using training sets (which makes up the highest percentage or ratio of the entire datasets). The process of training allows models to learn overtime by adjusting output to desired output using loss function. Supervised ML are mostly used for solving either regression or classification problems. Some of the ML algorithms use for classification of data into 2 or more groups include Neural Networks (NNs) Support Vector Machine (SVM) and Naive Bayes classifier. For regression tasks, Linear regression, Random Forest, Decision Tree are mostly used [44-45].

Unlike supervised ML that use labelled data and required human intervention, unsupervised ML employ unlabeled data where algorithms are run to discover hidden patterns in datasets and produce output by either clustering data that share same features or classifying them into groups. One of the advantages of unsupervised ML is that it doesn't require human intervention (in terms of classifying data). The ability of unsupervised ML to identify differences and similarities in data make them suitable for complex image recognition, segmentation, exploratory data analysis etc. Unsupervised ML algorithms are crucial for identifying patterns in complex data or data that contain multiple features or properties. Thus, clustering algorithms are the most common type of unsupervised ML. Some common examples of unsupervised ML models include Gaussian mixture, K-means, Principal Components Analysis (PCA) etc. [44-45].

Reinforcement ML differs significantly with both supervised and unsupervised ML. The concept of reinforcement ML revolves around "trial and error" which result in "reward and punishment". Reinforcement ML algorithm learn to perform tasks by perceiving and interpreting its environment. An example of reinforcement ML algorithms include Q-learning, Deep Q-networks, State-action-reward-state-action (SARSA). Despite the fact that the field of reinforcement ML has been a topic of interests for computer and robotics technologies, however, its real-world application and adoption is hindered by so many challenges such as difficult to deploy, the stage need for preparing the simulation environment, the need for expensive computer applications and resources etc. [46-47].

3.3 Deep Learning (DL)

Deep learning is a subset of ML that mimic human cognitive system where neurons interact with each other. DL architectures are designed based on stacking multiple perceptron which contain 3 layers namely, input, hidden and output layers. These layers are stacked in hierarchal order of increasing abstraction and complexity unlike conventional ML models that are linear [48].

Convolutional Neural Networks (CNNs) and Artificial Neural Networks (ANNs) are the 2 most popular DL networks which are used in image classifications, speech recognition, prediction etc. The models (designed using multilayer perceptron or networks) are trained using substantial amount of data which is crucial for attaining high performance in terms of accuracy and top-error. The training process allow the models to learn parameters through a process known as back propagation or gradient descent. This process revolves around the optimization of the difference between predictive value and actual value. The first cycle of training process is guarantee to result in an error output. Thus, gradient descent function by optimizing predictive output to attain actual output by adjusting both weights and biases [48-49].

For the past decades, scientists have developed several DL models, however, some of these architectures have performed better than others in the ImageNet Large-Scale Visual Recognition Challenge (ILSVRC) which include AlexNet, VGGNet, GoogleNet or Inception and ResNet as shown in Table 2. Other popular architectures include DenseNet, MobileNet, SqueezeNet etc.

Table 2. Top-performing DL architectures in the ILSVRC

Networks	Layers	Developers	Activation Function	Classifier	Accuracy (%)	Top-5 error (%)
AlexNet	8	Alex Krizhevsky, Geoffrey Hinton and Ilya Sutskever	ReLu	SoftMax	84.7	15.3
VGGNet	16 and 19	Andrew Zisserman and Karen Simonyan	ReLu	SoftMax	92.68	7.32
GoogleNet	22	Google Team	ReLu	SoftMax	93.3	6.67
ResNet	18, 50, 101 and 152	Microsoft Team	ReLu	SoftMax	95.5	4.5

*ReLu: Rectified Linear Unit

3.4 Transfer Learning (TL)

The concept of TL networks also known as pretrained networks have gained interests from scientists in the field of AI, computer scientists, data analysis in the last decades due to growing of data such as big data, cloud computing and the designed of several DL architectures. Currently, majority of scientists opt to use of TL models instead of developing models from scratch which require large amount of data for training and evaluation. TL can be defined as a branch of ML that seeks to apply knowledge or learned parameters (such as weights, biases, features) acquired from one task to a different but similar problem (target or new task [50-51].

One of the key points of TL approach is the “reuse” or “repurpose” of models previously trained using large amount of data (such as the ImageNet datasets) for solving problems on new task which contain fewer amount of data. Some of the advantage of using pretrained models include excellent performance time-savings, effort-savings, the use of small learning rates and low computation [51].

4. AI-Powered Detection of TB

Early and accurate diagnosis of TB is crucial for treatment and prevention. Medical experts such as Pathologists, Microbiologists and Radiologists rely lab-bench assays such as culture test, PCR and radiographic imaging (X-ray) for diagnosis of TB. Microscopic evaluation of MBTB using culture test and other staining approaches is regarded as the most widely approach employed by medical experts. The challenges revolving around this approach contribute to the high probability of miss-diagnosis. One of these limitations include the overlapping of MBTB against each other. Secondly, evaluating and interpreting large number of microscopic slides can be tedious and strenuous work even for experience Microbiologists. Thirdly, the small size (less than 1μm in diameter), heterogenous shape and irregular of MBTB as well as low background contrast and faint boundaries can also contribute to miss-diagnosis [52-53].

The use of radiographic images is another alternative, however, differentiating between lung diseases such as pneumonia and tuberculosis is very challenging. Despite the reliance of these approaches, there has been so many cases of miss-diagnosis, false positive results, irreproducibility, inaccuracy etc. In order to addressed these challenges, scientists adopted the use of computer aided approaches using AI-driven techniques. CAD have shown to aid medical experts in diagnosis of several diseases which include non-COVID-19 pneumonia, COVID-19 pneumonia, Cancer (breast, prostate, lungs, liver etc), skin diseases etc. [54-55].

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4.1 Microscopic Slide Images

The study conducted by Chang et al. [56] applied TL for the classification of TB. The study curated data from Tao-Yuan General hospital, Taiwan which contain 16,503 images from 1727 cases (1430 negative, 173 positive and 124 polluted). In order to addressed the issue of data imbalance, the study utilized SMOTE technique which synthesize new data from minority classes. The performance evaluation of the transfer learning deep learning model resulted in 98% recall and 99% precision.

The classification of TB and normal cases from MS images using TL based on pretrained AlexNet was proposed by Ibrahim et al. [41]. The study acquired image datasets from Near East university hospital which contain 530 images. In order to increase the performance of the model, the images were augmented via cropping and rotation (900, 1800 and 2700) resulting in 2444 images. The performance evaluation of the pretrained AlexNet model achieved 98.73% accuracy, 98.59% sensitivity and 98.84% specificity on unseen datasets. The study also conducted machine vs human comparison where machine outperform both beginners and expert microbiologists.

The use of CNN model built from scratch for the binary classification of TB into positive and negative manifestations was proposed by Xiong et al. [57]. The model named tuberculosis AI (TB-AI) is trained using 45 samples (15 negative and 30 positive cases) and tested using 201 samples (93 negative and 108 positive cases) collected from the Department of Pathology, Peking University First Hospital. The evaluation of the model performance was conducted based on evaluation metrics and comparison between TB-AI and human Pathologists. The result indicated that TB-AI achieved 97.94% sensitivity and 83.65% specificity.

The study proposed by El-Melegy et al. [58] deployed DL model for the classification and localization of mycobacterium tuberculosis in conventional ZN-stained microscopic images. The research utilized 500 microscopic stain images which are partition into 80% for training and 20% for testing and validation. The images are trained and tested using Faster-region-based convolutional neural network plus CNN (F-R-CNN+CNN) and Region-based convolutional neural network F-R-CNN. The performance evaluation and comparison of the deep CNN models revealed that F-R-CNN+CNN achieved the best result with 98.4% accuracy and 85.1% sensitivity.

The study conducted by Khan et al. [59] applied ANN for the prediction of TB from TB suspected cultured images. The dataset is generated from samples collected from TB suspects referred to the center, care takers and guardians between 2016 to 2017. The model is trained, tested and validated using 12,636 records including other features such as TB history, HIV status, age, gender, signs and symptoms. The performance evaluation of the applied ANN resulted in greater than 94% overall accuracy on training dataset and greater than 93% accuracy on both validation and test sets.

The study conducted by Quinn et al. [60] applied DL model on 3 microscopic images which include the detection of TB from sputum samples as well as malaria from thick blood smears and intestinal parasites eggs from stool samples. The CNN model is designed using an input layer, 4 hidden layers and output layer with 500 hidden units. The model is trained and validated using 315,142 test patches. The performance evaluation of the model resulted in an AUC value of 0.99.

The application of DL network and segmentation for the classification of TB was proposed by Costa et al. [61]. The study generated 120-sputum-smear microscopy slices of 12 patients which are processed using 3 filters to differentiate the bacilli from artifact. Identification of bacillus is carried out based on image acquisition, segmentation (using SVM and neural networks classifiers) and post-processing. The result of the use of DL network for the identification of bacillus achieved an overall sensitivity of 96.80% and an error rate of 3.38%.

The study conducted by Muyama et al. [62] applied 2 TL models which include GoogleNet and InceptionV3 for the classification of TB from ZN sputum smear slide images. The models are fed with the combination of dataset accessible from online repository and the ones captured using cell phone's camera in the university microbiology laboratory (with 143 images). The 2 datasets are combined together and split into 80% for training, 20% for testing and validation. The training of the models conducted based on find-tunning, without augmentation and with augmentation. However, among all the pre-trained models, InceptionV3 achieved the highest accuracy score of 86.7%. The summary of the application of DL for classification of TB from Microscopic slide images are presented in Table 3.

Table 3. Application of DL for the Classification of TB from Microscopic Slide Images

Reference	Model	Dataset	Result
[56]	Pretrained Model	16,503	98% recall and 99% precision
[41]	Pretrained AlexNet	530	98.73% accuracy, 98.59% sensitivity and 98.84% specificity
[57]	Tuberculosis-AI (TB-AI)	246	97.94% sensitivity and 83.65% specificity
[58]	F-R-CNN+CNN	500	98.4% accuracy and 85.1% sensitivity
[59]	ANN	12,636 records	93% accuracy
[60]	CNN	315,142 test patches	0.99 AUC value
[61]	Neural Networks classifers and SVM	120 sputum samples	96.80 overall sensitivity
[62]	InceptionV3	143 Ziehl Nelsen-stained images	86.7% accuracy

*AI: Artificial Intelligence; AUC: Area Under the Curve; CNN: Convolutional Neural Network SVM: Support Vector Machine; TB: Tuberculosis

4.2 Radiographic Images

The classification of X-ray images of TB and normal cases using deep learning models was proposed by Faruk et al. [63]. The study applied 4 different CNN models which include InceptionResNet2, InceptionV3, MobileNetV2 and Xception for the classification of X-ray images curated from publicly accessible dataset. In order to increase the number of training dataset, the study conducted data augmentation. The models are trained using 70%, tested using 20 % and validated using 10% of the datasets. The performance evaluation of the TL models based on several metrics has shown that InceptionResNetV2 achieved the best result with 99.12% training accuracy, 99.36% validation accuracy, 98% precision, 99% recall and 99% F-1 score.

In order to improve the prediction performance of larger dataset using DL, Duong et al. [64] proposed the use of 3 platforms or engines which include optimized original vision transformer, optimized EfficientNet and hybrid system (of both vison transformer and EfficientNet) for the classification of chest X-ray of TB datasets curated from different public accessible domains. The study partitions the dataset into training, testing and validation. The result has shown that hybrid model achieved the best performances with 97.72% accuracy and 100% AUC.

The use of TL based on pretrained AlexNet for the classification of Chest X-ray images of TB and healthy cases was proposed by Abbas et al. [65]. One of the distinctions of this study is the application of different tuning which include shallow-tuning, deep-tuning and fine-tuning of the models. The study curated 138 images which are augmented in order to increase training datasets, improve contrasts and quality of the surface tissue. The model was trained using 70%, validated using 20% and tested using 10% of the datasets. The evaluation of the model performance based on AUC, sensitivity and specificity rate has shown that fine-tuning of the model achieved higher result with 0.998, 0.999 and 0.997 AUC, sensitivity and specificity respectively.

The study conducted by Pattanasuwan and Chongstitvatana [66] applied 4 pretrained CNN models for the classification of chest X-ray images into TB and normal cases. The study utilized DenseNet, EfficientNetB0, ResNet50 and VGG16 on collection of 3 different datasets collected from Shenzhen, Bureau of TB and Montgomery (1743 total images). The result of evaluation metrics adopted indicated that DenseNet achieve the best performance with 91% accuracy, 92% recall, 91% precision and 95% AUC. The study proposed by Hwang et al. [67] developed a computer aided detection of TB using TL approach. The model is trained using 3 different datasets containing both positive and negative chest X-ray images. The result of the model performance yield 0.88, 0.93 and 0.96 AUC values for the 3 respective datasets.

The use of quantum-based TL approach based on AlexNet, DenseNet169 and VGG19 for the classification of X-ray images of TB and healthy cases was proposed by Mogalapalli et al. [68]. The models are trained and tested using different classifications of datasets which include TB, Trash and Crack with total number of 662 non-TB and TB cases. The performance evaluations of the models have shown that in terms of accuracy, AlexNet exhibit better performance of on TB datasets with 89.55%, 89.82% precision, 89.6% recall, 89.54% F1-score. The study conducted by Ravi et al. [69] applied 26 different pretrained networks for 3-way classification of X-ray images into TB, non-TB and sick but non-TB. Among these 26 pretrained networks 7 are EfficientNet (ENet)-based CNN models which have shown to performed better than the rest Pretrained CNN models with accuracy above 99% after 15 epochs.

The study conducted by Lakhani and Sundaram [70] proposed the use of CAD for the classification of pulmonary TB and healthy manifestations using chest radiographs. Training (68%), validation (17.1%) and testing (14.9%) of 1007 posteroanterior chest radiographs (curated from 4 deidentified HIPAA-compliant datasets). Prior to training, the acquired datasets undergo preprocessing stages and augmentation to yield more training sets. The images were trained and tested using both pretrained, untrained and ensembled deep convolutional neural networks (DCNNs) which include GoogleNet and AlexNet. The comparison of the performance evaluation between single models and ensembled models has shown that ensembled models (GoogleNet and AlexNet) achieved the best result in terms of AUC with 0.99. Moreover, the result also revealed pretrained models perform better than untrained ones.

The study proposed by Rahaman et al. [71] applied 9 pretrained networks for the classification of TB and healthy cases from chest X-ray images. The study carried out several process which include image preprocessing, data augmentation, segmentation and classification. The study curated 7000 images (3500 each for TB and non-TB) from different public domains which are trained and tested using 3 types of ResNet (18, 50 and 101), CHeXNet, DenseNet201, Inceptionv3, MobileNet, SqueezeNet and VGG19. In order to evaluate the best approach, the study conducted 3 distinct experiments which include the use of U-net models for the segmentation of X-ray images, classification using X-ray images and classification using segmented images. The best result is achieved using DenseNet201 for the classification of segmented images with 98.6% accuracy, 98.56% sensitivity, 98.54% specificity, 98.57% precision and 98.56% F-1 score. The summary of the application of DL for classification of TB from X-ray images are presented in table 4.

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Table 4. Application of DL for Classification of TB from X-ray images

Reference	Model	Dataset	Result
[63]	InceptionResNetV2	-	98% precision, 99% recall and 99% F-1 score
[64]	Hybrid system (vison transformer and EfficientNet)	-	97.72% accuracy and 100% AUC
[65]	Pretrained AlexNet	138	0.998, 0.999 and 0.997 AUC, sensitivity and specificity
[66]	DenseNet	1743	91% accuracy, 92% recall, 91% precision and 95% AUC
[67]	TL	-	0.88, 0.93 and 0.96 AUC value
[68]	Pretrained AlexNet	662	89.55%, 89.82% precision, 89.6% recall, 89.54% F1-score
[69]	EfficientNet (ENet)-based CNN	-	99% accuracy
[70]	Ensembled GoogleNet and AlexNet	1007	0.99 AUC
[71]	DenseNet201	7000	98.6% accuracy, 98.56% sensitivity, 98.54% specificity, 98.57%

*AUC: Area Under the Curve

5. Architecture and framework IoT/AI-enabled System

The proposed IoT enabled system relies on the integration of three systems; namely medical imaging devices (X-ray machine, digital microscope), AI-driven models and IoT system. The framework of the proposed system is based on collecting images of suspected patients are feeding the images into DL models.

5.1 Medical Imaging

The use of imaging for diagnosis in healthcare systems revolves around medical imaging also known as radiology and other type of images generated for medical devices such as microscope. Medical imaging technology allow medical expert to recreate various images of human body for diagnostics purposes. Medical imaging can be categorized as traditional medical imaging which comprises of X-ray, MRI, endoscopy, ultrasound and CT scan and nuclear imaging which comprises of Spectro Emission Computed Tomography (SPECT) and Position emission Tomography (PET). Other imaging techniques include the ones related to recoding electrical activity of the body part such as electrocardiograph, electroencephalographs etc. The integration of AI and computer vision with medical imaging is enhancing the technology by aiding medical experts to interpret images accurately, reduce the probability of miss-diagnosis, increase time-saving and effort-saving [72-74].

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5.2 Artificial intelligence models

The use of AI is one of the key factors that is transforming healthcare system. AI driven approaches have been applied in solving problems related to vital signs of symptoms for generation of biomedical data for decision making using predictive methods and modeling. Medical expert and computer scientists and engineers are working together to developed new approaches using computer software, AI, IoT and medical data, data mining for diagnosis of diseases such as pneumonia, TB, cancer, cardiovascular diseases and genetic diseases. The increase in amount of biomedical data in databases and cloud computing has allowed scientist to use different machine learning models [75].

5.3 Internet of Things (IoT)

IoT is a network which integrates internet, sensors, communication networks, intelligence operations and processing, transmission technologies and other perceptive technologies which are connected to a physical device. IoT system use Radio Frequency Identification (RFID) and wireless connection to communicate with devices and humans. The architecture of IoT system consist of 3 layers namely; perceptual layer, network layer and application layer. The perceptual layer comprises of sensor and sensor network, the next layer which is the network layer consists of the internet and mobile communication network while the third layer which is the application layer is where intelligent operations and processing were carried out [76-77].

The integration of IoT, artificial IoT and sensors contributed to the advancement of smart systems that can be used to detect, manage and control diseases. The use of smart sensing tools and monitoring devices designed using chips and sensors improved various aspect of healthcare systems in terms of detection of pathogens that causes disease, monitoring of medication, storage and analysis of vital signals, medical records management and rehabilitation of diseases [78].

5.4 Supporting Researches

The study conducted by Rodrigues et al. [79] proposed the use of IoT/DL/TL approach for the detection of skin lesions, melanoma and typical nevi. The study combines different ML techniques such as ResNet, DenseNet, MobileNet and classifiers such as SVM, Random Forests, K-Nearest Neighbor, Perceptron Multilayer etc. The mechanism behind the working principles of the proposed IoT-assisted system revolves around the use of online application to upload skin image of patients by a physician followed by data extraction and classification using DL models.

Iskanderani et al. [80] proposed and IoT/AI platform for the detection of COVID-19 from Chest X-ray images. The proposed system offers real-time communication and detection of COVID-19 cases. The platform is designed by assembling 4 DL models which include DenseNet201, VGG19, InceptionResNetV2 and ResNet152V2. The working principle of the framework revolves around the use of medical sensors to obtained CXR images which are fed into the ensemble networks for classification. Similarly, Kini et al. [81] proposed the use of IoT-DL-based framework for the diagnosis of COVID-19 from CT scan images. The system is designed to collect CT scan images using medical IoT devices which transferred the images to an ensembled model (which combines 3 pretrained networks which include DenseNet201, InceptionResNetV2 and ResNet152V2). The ensembled model was able to classified CT scan images efficiently on IoT servers.

Le et al. [82] proposed an IoT-enabled depth-wise separable CNN merged with deep SVM for the classification of COVID-19 from X-ray images. The process is dictated by several stages which include data acquisition using IoT devices which send the images to cloud server, followed by Gaussian filtering to remove noise, feature extraction and finally classification. Another IoT/DL-enabled framework was proposed by Ahmed et al. [83]. The X-ray images are collected using medical sensors followed by detection using Faster Region CNN (FR-CNN) and ResNet101 as the backbone network.

5.5 Mechanism

Inspired by the supporting researches, our proposed framework is aim to developed a system which allow transfer of medical images from X-ray devices and digital or electronic microscope to computer trained using DL models for the classification of TB and non-TB cases. Subsequently the result of the classification can be store in a cloud or shared with end users such as patients or doctors as shown in Figure 3. There are different types of ML models, however, the use deep neural networks such as CNN and recurrent neural network (RNN) models have proven to be an efficient approach for classification and prediction of biomedical data.

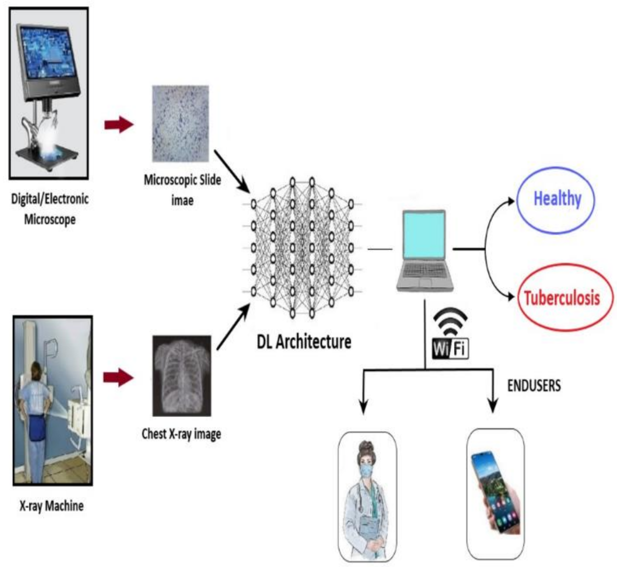

Figure 3. Architectural Framework of Proposed IoT/AI-enabled System

6. Open Research Issue

Despite the growing trends of the use of AI-driven models and CAD in screening and classifying medical images of patients. The technology is still hindered by several challenges which need to be address in order to reach its full potential. CAD technology is fuel by data. Therefore, training AI-driven model is crucial for increasing accuracy as long as overfitting is addressed. The growing trend in cloud computing and big biomedical data continue to offer scientists with larger amount and diverse type of data [84]. Currently there are several repositories that provide various data such as Kaggle and GitHub. Moreover, scientists adopted several data augmentation techniques which produce larger amount of training set through rotation, zooming, flipping, cropping etc. Despite the availability and accessibility of data and data augmentation, developing models from scratch still require hundred thousand of images to become more efficient and reliable [85-86].

The concept of TL has attempted to address this issue where pretrained models that are trained using hundred thousand of images are repurpose on classification task with limited amount of data. However, TL has its own limitations which include unification, effective ways of measuring knowledge gain, the use of dissimilar datasets [87]. Another challenge limiting ML and DL algorithms is low interpretability. This problem can be attributed to tremendous amount of the parameters of the DL models and complex calculating process. Thus, it is difficult to comprehend how these models work or arrive at a final output similar to human interpretation which is why they are termed as so-called black boxes [88].

The application of biomedical data (such as radiographic images, slide images, biosensing signals, wearable devices results and other output generated from medical devices) are limited by complexity and privacy. Due to data complexity of medical data, scientists adopted several pre-processing and conversion techniques in order to generate desirable input, reduce complexity, enhance resolution etc. Privacy of medical data is another serious challenge that is facing the use of clinical and diagnostic data for classification, prediction and decision making. Medical data are less readily available for scientists to train and validate DL models. Thus, appropriate policies are required in order to overcome ethical, commercial, legal and societal barriers that limit the use of medical data for ML and DL applications [89].

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.1. Subsection

3.1.1. Subsubsection

Bulleted lists look like this:

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1. First item;
2. Second item;
3. Third item.

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3.2. Figures, Tables and Schemes

All figures and tables should be cited in the main text as Figure 1, Table 1, etc.

Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited.

Title 1	Title 2	Title 3
entry 1	data	data
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5. Conclusions

The cases of TB continue to reck havoc and instigate healthcare challenges especially in remote areas and poor communities with limited medical resources or lack advanced medical devices. Early detection of active TB cases is crucial for timely management and controlling the incidence and spread of the disease. Scientists rely on several approaches for the detection of TB which include Tuberculin test, culture test, GeneXpert, X-ray imaging etc. However, microscopic examination using culture and staging techniques as well as X-ray imaging are among the most adopted approaches for TB especially in remote regions.

Despite the wide reliance of these techniques, they are hampered by several challenges such as inability to differentiate between resistant and non-resistant type, false positive results, miss-diagnosis, tediousness, workload etc. Therefore, it is crucial to develop an ideal diagnosis approach that is accurate, fast, cheap and efficient. In order to address these challenges, computer scientists along with medical expert developed CAD approach which integrate medical imaging and ML models such as CNNs developed from scratch and pretrained networks. Models developed or applied for detection of TB such as AlexNet, ResNet, VGGNet, Inception models, DenseNet, CheXNet etc are becoming more refined and streamlined. Several studies have reported the outperformance of ML models against human experts.

The integration of IoT in healthcare is transforming the sector into a more digitized and smart system. The current COVID-19 pandemic has led scientists to developed an AI/IoT-based system that allow users to upload chest and CT scan images for classification of TB in real-time. This study proposed similar approach where the system receive radiographic and microscopic slide images as input for DL models and the subsequent classification output can be transferred to end users such as patients or physicians or can be store in cloud or hospital data storage system.

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Conflicts of Interest: We declare conflicts of interest or state

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References must be numbered in order of appearance in the text (including citations in tables and legends) and listed individually at the end of the manuscript. We recommend preparing the references with a bibliography software package, such as

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