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Review

Current Technologies for Detection of COVID-19: Biosensors, Artificial Intelligence and Internet of Medical Things (IoMT): Review

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Abstract: Despite the fact that COVID-19 is no longer a global pandemic due to development and integration of different technologies for the diagnosis and treatment of the disease. Technological advancement in the field of molecular biology, electronics, computer science, artificial intelligence, Internet of Things, nanotechnology etc. has led to the development of molecular approaches and computer aided diagnosis for the detection of COVID-19. This study provides a holistic approach on COVID-19 detection based on (1) molecular diagnosis which include RT-PCR, antigen-antibody and CRISPR-based biosensors and (2) computer aided detection based on AI-driven models which include Deep Learning and Transfer learning approach. The review also provide comparison between these 2 emerging technologies and open research issues for the development of smart-IoMT-enable platform for the detection of COVID-19.

Keywords: Biosensors; COVID-19; Artificial Intelligence; Computer-aided Detection (CAD) Internet of Medical Things (IoMT)

1. Introduction

The year 2020 has witnessed massive global burden due to the spread of pneumonia causing virus known as SARS-CoV2 or COVID-19. The disease has led to massive screening, quarantines, restriction of movement, closure of land and borders, lock downs, closure of educational, sportive and entertainment centers and force people to work from home [1]. In order to control the disease, scientists from different field work hand in hand together to developed diagnosis approaches, prediction models, treatment control strategies, vaccines etc. Screening of SARS-CoV-2 using lab-bench assay is regarded as the first line of action in terms of minimizing spread and early treatment of the disease. This prompted the Chinese government to enact several testing points [2].

Medical experts rely on 2 main molecular approaches which include RT-PCR and antibody-antigen based techniques for the detection of the disease. However, among these two molecular testing approaches, RT-PCR is regarded as the gold standard technique due to it specificity and accuracy. The tests allow healthcare experts to detect viral nucleic acid from patient samples collected using nasal swab which is amplified using PCR machine. Antigen-antibody revolves around the binding between synthesized recombinant antigen and the antibodies present in the body which elicit antigen-antibody reaction [3-4].

Despite the higher specificity of these molecular approaches, they are hindered by several challenges which include false positive results which can lead to miss-diagnosis and expensive especially in underdeveloped countries. As an alternative, healthcare professionals employ radiographic screening using X-ray imaging and CT-scan imaging which allow scientists to discriminate between positive and negative cases. Others employ these techniques as a follow up approach or confirmation tests. As a result of massive or large-scale screening of radiographic images, these techniques can be tedious for radiologists and can led to miss-interpretation [5-7].

In order to address these issues, scientists merge radiographic imaging with computer applications to developed computer aided diagnosis which allow screening of thousand images with high accuracy, precision and specificity [8-9]. CAD has shown to aid medical experts in the past for the detection of different types of cancer such as breast cancer [10], colon cancer [11], prostate cancer [12], tuberculosis [13], bacterial pneumonia [14], non-COVID-19 viral pneumonia [15], skin disease [16].

The integration of IoT in medical care known as IoMT is changing the landscape of patient care, diagnosis and treatment. IoMT revolves around the interconnection between medical devices using internet. The platform enables machine-machine communication, patient-machine communication, machine-medical professional communication etc. An example of IoMT system include patient tracking devices, remote patient monitoring, medication tracking devices etc. [17-19].

The prospect of smart diagnosis has been gaining ground in the last decade. The integration of smart technologies such as AI and IoMT with conventional diagnosis approaches has the potential to improve diagnosis, real-time or point of care detection, minimize errors and allow sharing of medical data between devices, end users and hospital cloud system [20-21].

1.1 Comparison with Similar Studies

Detection of COVID-19 has been crucial for treatment and controlling the spread of the virus. Scientists employ several emerging technologies which include the use CAD based on AI driven models, AI/IoT enabled systems and molecular testing based on RT-PCR and CRISPR/Cas based biosensors. Innumerous studies in the literature only concentrated on one of these emerging technologies. However, this study evaluated each technique separately and compare them in terms of cost, performance (accuracy, sensitivity, specificity) deployment etc.

The review provided by Samson et al. [22] focused on the application of biosensing technology for the detection of COVID-19. The review discusses about nucleic acid-based biosensors such as CRISPR/Cas9 strip-based biosensor, aptamer-based biosensors, surface plasmon resonance, antigen-Au/Ag nanoparticles-based biosensors as well as existing challenges and future perspectives. However, the review differs with the current study in terms of radiographic detection of COVID-19, AI-powered detection and IoT-enable detection of COVID-19.

The study conducted by Santiago [23] presented trends and innovation in biosensing technology for the detection of COVID-19. The study covers several molecular testing approaches which include antigenic and serological rapid testing as well as CRISPR-based biosensors. However, the study does not cover the use of medical imaging technology for the detection of COVID-19, Computer aided detection and IoT-enabled detection of COVID-19.

Another review that focusses on molecular and conventional testing was provided by Falzone et al. [24]. The study covers wide range of diagnostic assays ranging from rapid antigen testing, antibody-based detection, immunoenzymatic serological testing, RT-PCR. Other techniques covered include CRISPR/Cas-based approaches, nucleic acid amplification techniques, digital PCR methods. The review also covers challenges and future perspectives.

The review conducted by Huang et al. [25] focuses on the application of AI-Powered detection of COVID-19 (which include ML, DL and TL) using medical data such as electronic medical records, medical images (X-ray, CT scans and Ultrasound). The review also highlighted on current challenges and future perspective. Some of the topics not covered include molecular testing, biosensing technology, IOT-enabled detection and comparison between AI-powered systems and biosensors.

Table 1. Comparison with similar studies

Ref	**COVID-19 pandemic**	**Molecular Diagnostic and Biosensors**	**Medical Imaging**	**AI, ML, DL and TL**	**IoT/IoMT**	**Comparison**	**Open Research Issue**
[22]	✓	✓	-	-	-	-	✓
[23]	✓	✓	-	-	-	-	-
[24]	✓	✓	-	-	-	-	✓
[25]	✓	-	✓	✓	-	-	✓
Our Report	✓	✓	✓	✓		✓	✓

1.2 Scope

The main aim of this review is to provide holistic approach on emerging technologies that aid in the detection of COVID-19 such as RT-PCR, antigen-antibody and CRISPR-based biosensor as well as computer aided detection using AI-driven models. Moreover, the review also covers the integration of IoMT and AI for the development of smart system for the detection of the disease.

Chapter 2 discusses about COVID-19 pandemic. Chapter 3 present an overview on molecular approaches for the detection of COVID-19 using RT-PCR and CRISPR-based biosensors. Chapter 4 discusses about computer aided detection of COVID-19 from radiographic images. Chapter 5 presents diagnostic imaging which include X-ray and CT scan. Chapter 6 discusses about comparison between molecular approaches and computer aided detection as well as smart AI/IoMT-enable platform for the detection of the disease. Chapter 7 discusses about open research issues and concluding remark

2. COVID-19

For the first time in a century the world witnessed another global pandemic caused by a coronavirus known as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2. The virus is traced back to sea food market in Wuhan, Hubei province China in the late December 2019. Coronavirus are positive single stranded RNA viruses which belong to the Coronaviridae family which also include SARS-CoV-1 and MERS-CoV. Both the 2 coronaviruses have caused epidemics and endemics in the last few years [1, 26].

SARS-CoV-1 is first identified in the year 2003 in China where bats are regarded as the main reservoirs. The virus has spread to 4 other countries causing global epidemics. SARS-CoV-1 affected close to 8000 people with approximately 10% mortality rate. The

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World Health Organization along with other international and non-Governmental organizations collaborated together to control and prevent further spread of the virus [27-28].

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is another virus that belong to Coronaviridae family that caused global burden in the year 2012. The virus is first identified in Saudi Arabia and later spread to 27 countries leading to approximately 2600 cases. The disease has infected over thousand and approximately 35% of patients died from the disease. Dromedary camels were linked with the transmission of the virus to human primates [29-30]. Table 2 shows the differences and similarities between SARS-CoV-1, MERS-CoV-2 and SERS-CoV-2 in terms of number of cases, fatality rate, mortality rate, reservoir etc.

Table 2. Comparison between SARS-CoV-1, MERS-CoV-2 and SERS-CoV-2

Coronavirus	Year	Reservoirs	Number of Cases	Number of deaths	Fatality rate
SARS-CoV-1	2003	Bat	>8000	780	~10%
MERS-CoV	2012	Dromedary Camels	26000	894	34.5%
SARS-CoV-2	2019	-	>633 million	>6.5 million	10%

2.1 Transmission of SARS-CoV-2

Unlike previous coronavirus disease that are associated with animal transmission such as bat in SARS-CoV-1 and dromedary camels in MERS-CoV, however, no animal reservoir has been found for SARS-CoV-2 [31]. Several studies have shown that the virus can be spread directly from one person to another (Human-human transmission) via sneezing, coughing or indirectly such as coming in contact with surface infected with the virus [31-32].

2.2 Symptoms of SARS-CoV-2

The clinical spectrum of COVID-19 disease ranges from asymptomatic to severe acute respiratory disease and death. People infected with the disease display pneumonia symptoms which include shortness of breath, sore throat, fever, fatigue, cough. People that are of risks of COVID-19 include elderly people who are suffering from chronical disease such as chronic lung disease, cancer, hypertension, renal and kidney diseases, diabetes, cardiovascular diseases etc. [32-33]. The clinical manifestation of SARS-CoV-2 is presented in Figure 1.

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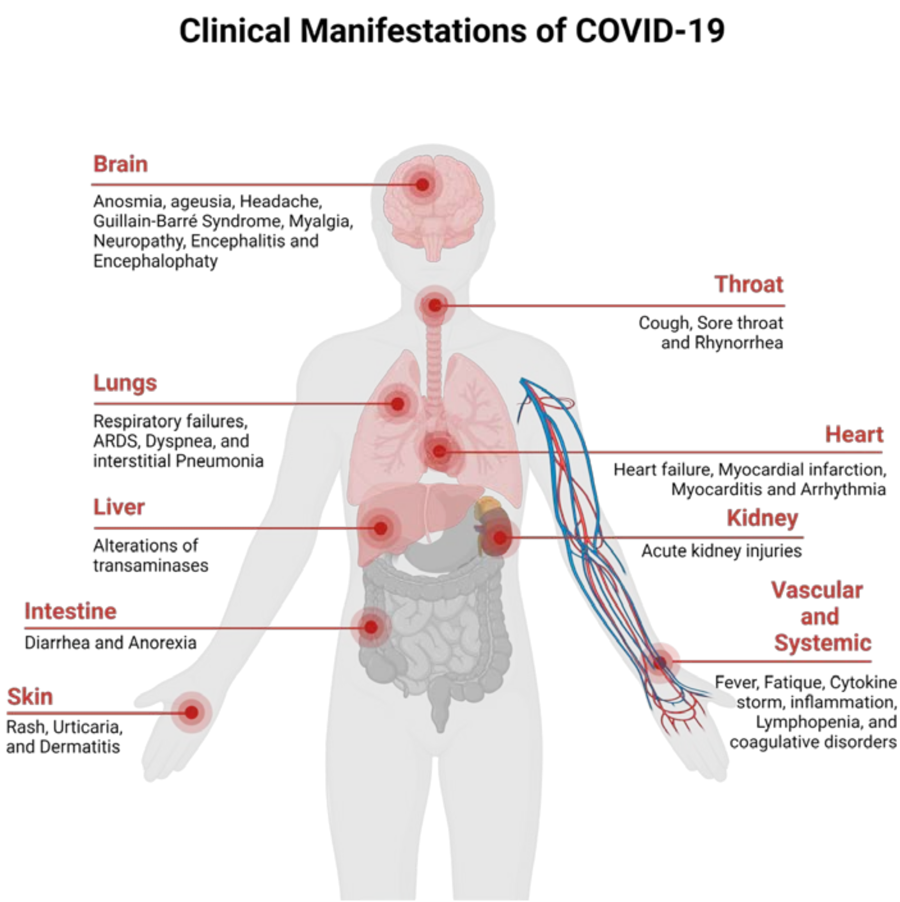

Figure 1. Clinical Manifestation of COVID-19

3. Molecular Diagnosis of COVID-19

Early and accurate detection of COVID-19 disease is crucial for timely management and prevention. The field of disease detection has been transformed from conventional diagnosis such as microscopy with lower sensitivity and specificity to molecular diagnosis such as antigen-antibody, enzyme-substrate and NA probe-target and biosensing technologies [3, 34] as shown in Figure 2. Diagnostic imaging based on CT scan, X-ray and Ultrasound imaging are currently use as an alternative or confirmatory approach for the detection of COVID-19 [35-36].

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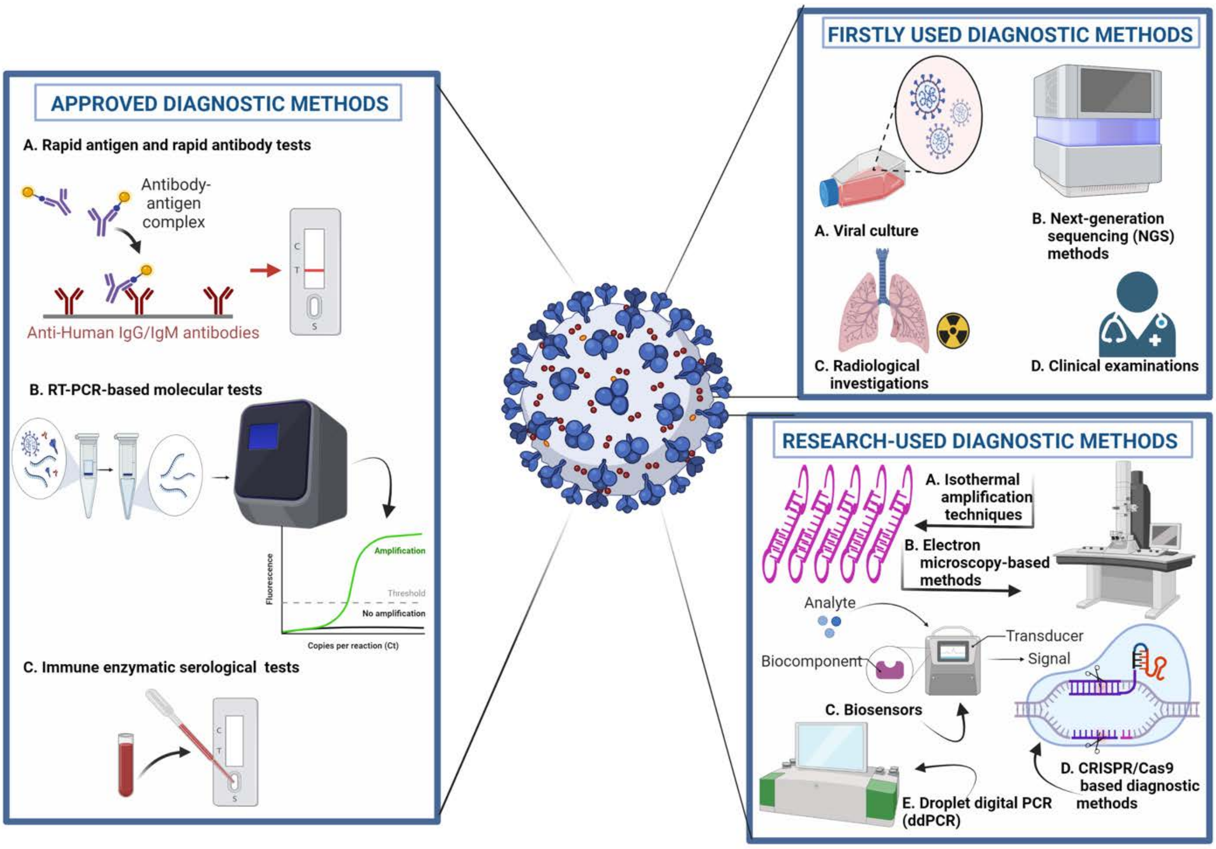

Figure 2. Molecular diagnostic approaches for the Detection of COVID-19. 1. Approved Diagnostic Methods; (a) Rapid Antigen and Rapid Antibody Tests; (b) RT-PCR-based Molecular Tests; (c) Immune Enzymatic Serological Tests. 2. Firstly Used Diagnostic; (a) Viral Culture; (b) Next Generation Sequencing (NGS) Methods; (c) Radiological Investigation; (d) Clinical Examination; 3. Research-used Diagnostic Methods; (a) Isothermal Amplification Techniques; (b) Electron microscopy-based Methods; (c) Biosensors; (d) CRISPR/Cas9-based Diagnostic Methods

3.1 Laboratory Assays

3.1.1 RT-PCR

RT-PCR is regarded as the most reliable approach for the detection SARS-CoV-2 [3,6, 37]. RT-PCR is a nuclear-derived approach for the detection of genetic content of pathogens such as viruses (such as Zika and Ebola) and bacteria. The early RT-PCR testing employ radioisotope markers which are subsequently replaced by fluorescent dyes. As shown in Figure 3, the procedure for conducting RT-PCR test follow 4 steps:

Sample collection: Nasal swab and nasopharyngeal samples are collected by medical experts. The samples are sealed and transported to the laboratory for detection.

Extraction: This step allows medical technologies to extract or isolate viral NA. This stage revolves around the use of chemicals to remove component such as fats and proteins.

PCR: The isolated viral NA is further amplified using PCR machine also known as thermal cycler. PCR machines amplified thousand complies of the viral NA which increase sensitivity and specificity of detection. Reverse transcription is carried out in order to convert RNA strands of the virus to DNA.

Detection: After the RNA is transcribed to DNA and amplified, the machine detects the presence of virus DNA due to the release of fluorescent dye which can be measured in real-time and presented in the computer screen.

RT-PCR method is highly specific and sensitive compare to antigen-antibody method. The test can take between 3-6 hours to process and obtained results. Moreover,

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this approach has shown to be faster, reliable and present lower rate of errors of false positive results compare to other approaches. One of the disadvantages of RT-PCR is that it can't be used to identify past diseases which is crucial for understanding the pathology and spread of the diseases [38-39].

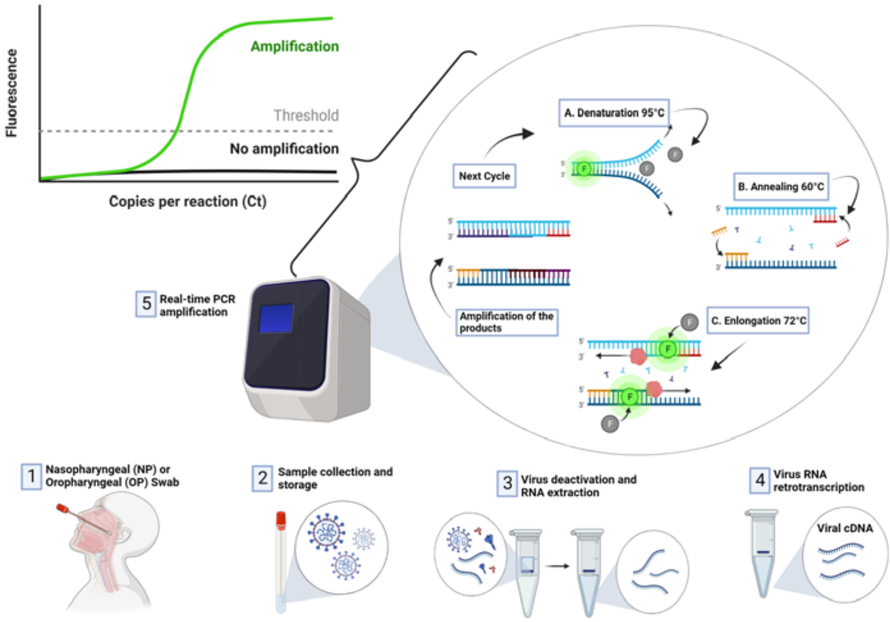

Figure 3. Detection of COVID-19 using RT-PCR Technique

3.1.2 Antibody-based Method

The emergence of SARS-CoV-2 has prompted scientists to developed viable diagnostic assays that can accurately detect the presence of the virus from biologically derived samples. Antigen-antibody approach as the second standard approach revolves around the binding between synthesized recombinant antigen (produced in the laboratory which mimic specific structure of SARS-CoV-2) and the antibodies present in the body which elicit antigen-antibody reaction. Unlike the RT-PCR, the specificity of antigen-antibody testing approach relies on the affinity of target antigen designed. Therefore, designing antigen specific to antibodies produced as a result of the present of the virus is crucial for increasing specificity and minimizing the probability of false positive results [40-41].

3.1.3 Antigen-based Method

COVID-19 antigen test is another popular diagnosis approach use as an alternative to RT-PCR approach. This test is mostly use for early detection of the disease and determining if patient is contagious. COVID-19 antigen testing revolves around the use of different type samples which include oral, nasal, respiratory tracts. One of the advantages of this approach is it is very easy to operate and can be used for early detection (i.e., 2 days before the onset of the symptoms). Antigen-based method can be divided into lateral flow rapid-test cassette format and enzyme-linked immunosorbent assay (ELISA) [41-42].

Lateral flow assay-based COVID-19 antigen test also known as antigen rapid test revolves around the collection of plasma, serum or blood bleed from the fingertip of suspected person which is subsequently transfer to the test cassette. The test lasted for 20 minutes where the result is display. Compare to lateral flow assay, ELISA-based COVID-19 antigen test produce accurate and more reliable result. One of the disadvantages of this approach is the requirement of intensive laboratory procedure which can be challenging for remote areas with limited healthcare resources [41, 43].

3.2 Application of Biosensors for the Detection of SARS-CoV-2

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The application of rapid, ultra-sensitive and quantitative electrochemical biosensor for the detection of SARS-CoV-2 is proposed by Alateef et al. [44]. The biosensor is designed using gold NPs (AUNPs) which is capped with highly specific antisense oligonucleotide while the sensing probe was immobilized on a paper-based electrochemical device. The sensing mechanism revolves around the interaction between the antisense SSDNA and sensing probe which generate readout result that can be seen in hand-held reader. In order to analyze the sensing viability of the paper-based electrochemical biosensor, the developed platform was tested using clinical and vero cells infected with the virus. The performance evaluation of the biosensor resulted in sensitivity of 231 (copies μL-1)-1 and 6.9 copies/UL LOD. Subsequent testing of the device using both samples obtained from 22 patients tested with SARS-CoV-2 confirmed using RT-PCR and 26 healthy patients resulted in 100 accuracy, sensitivity and specificity.

The development of cheap CRISPR-based POC testing platform known as miSHERLOCK for the detection of SARS-CoV-2 was proposed by de Puig et al. [45]. The sensing mechanism revolves around the collection of unprocessed saliva, followed by extraction, purification, concentration, amplification and detection based on the interaction between viral NA and guide RNA bind with Cas12a produce fluorescent visual output within 1hr. The performance of the platform resulted in highly sensitive and multiplexed detection of the virus and mutations associated with 2 different variants leading to different LOD in cp/ml. Another distinction of this approach is the application of adjunct smartphones to enable quantification of output, automated interpretation, the prospect of remote and distributed result reporting.

Song et al., [46] developed antifouling electrochemical biosensor for the detection of SARS-CoV-2 NA. The nanobiosensor is designed based on electropolymerized polyaniline nanowires and synthesized Y-shaped peptide which poses antifouling properties. The mechanism behind the working principle of the biosensor revolves around the interaction between immobilized biotin-labeled probes and COVID-19 NA. Evaluation of the performance of the genosensor led to 3.5fM detection limit and wide linear range of 10-14 to 10-9 M.

Detection of SARS-CoV-2 from clinical sample using Field-effect transistor (FET)-biosensor was proposed by Seo et al. [47]. The biosensor was constructed by coating graphene sheet of the FET with specific antibody against the viral spike protein. In order to test the viability of the immunobiosensor, several samples such as antigen proteins, cultured virus and nasopharyngeal swab samples collected from patients suffering from COVID-19 pneumonia. The performance of the FET-based biosensor for the detection of SARS-CoV-2 spike protein yield 100 fg/mL concentration in clinical transport medium and 1 fg/mL concentration in phosphate buffer saline. The biosensor was able to detect SARS-CoV-2 in cultured medium with 1.6 X 101 pfu/mL LOD and clinical samples with 2.42 X 102 copies/ML.

Tian et al. [48] developed an electrochemical aptamer-based biosensor for detection of COVID-19. The biosensor was constructed using metal-organic frameworks MIL-53(AI) which is decorated using AU@Pt NPs and enzymes. The surface of the electrodes was immobilized with dual aptamer as biorecognition element. SARS-CoV-2 is detected based on the interaction between immobilized 2 thiol-modified aptamers (N48 and N61) and SARS-CoV-2 nucleocapsid via the co-catalysis of the nanomaterials, G-quadruplex DNAzyme and Horseradish Peroxidase (HRP). Evaluation of the biosensor demonstrated 8.33pg mL-1 LOD and wide linear range of 0.025 to 50ng ML-1.

Buyuksunetci et al. [49] developed an electrochemical biosensor for the detection of SARS-CoV-2. The device was constructed using gold screen printed electrode (AuSPE) and subsequently immobilized with either angiotensin-converting enzyme 2 or CD147.The biosensor is designed based on the interaction between spike protein with receptors such (ACE2) or CD147. Evaluation of the performance of the biosensor yielded 29930 ng ML-1 LOD and linear detection range of 700 ng ML-1 to 1500 ng ML-1 and 1500 ng ML-1 to 7000 ng ML-1 for the detection of spike protein using ACE2. While detection of spike protein using CD147 yielded 38.99 ng ML-1 LOD and linear detection ranges of 500 ng ML-1 to 5000 ng ML-1. The biosensor was also evaluated using clinical samples confirmed with RT-PCR method.

The development of multiplexed grating-couple fluorescent plasmonic biosensor for the detection of SARS-CoV-2 using either dried blood spot sample or human blood serum is proposed by Cady et al. [50]. Detection of COVID-19 relied upon the interaction between antibody (IgG) and antigen (nucleocapsid protein, Spike S1 and Spike S1S2). The performance evaluation of the immunobiosensor produced linear response for serum samples diluted to 1:1600 dilution. The biosensor was also compared with 2 commercial COVID antibody testing kits (which include Luminex-based microsphere immunoassay and ELISA) which resulted in 100% correlation. Moreover, 63 samples of dried blood spot were tested using the constructed immunobiosensor which yielded 86.7% sensitivity and 100% selectivity for detection prior to COVID-19 infection.

Kim et al. [51] developed a sensitive electrochemical biosensor for point-of-care detection of COVID-19. The genobiosensor was designed using multi-microelectrode array relied upon the interaction between probes and target genes (N gene and RdRP gene) amplified using Recombinase Polymerase Amplification (RPA) and subsequently detected using pulse voltammetry. This process involve hybridization between thiol-modified primers immobilized on the surface of WE and RPA amplicon which resulted in reduction of current density due to accumulation of amplicons. The performance of the assay yielded 3.925 fg/μL LOD for N gene and 0.972 fg/μL for RdRP gene.

4. Computer-aided Diagnosis and Internet of Medical Things (IoMT)

Computer aided diagnosis CAD is regarded as one of the technologies that is transforming medical diagnosis. This technology revolves around the use of computer applications, software, algorithms for detection of diseases that often require human expertise, prolong procedures, the use of chemicals or radiations etc [8]. CAD technology is driven by Machine Learning, Deep Learning as sub-field of ML and Transfer Learning which allow the transfer of knowledge learn from trained networks to perform similar function on different task. [52].

The field of medical diagnosis is undergoing transformation due to the integration of CAD, automated detection and smart sensing. Medical imaging based on diagnostic radiology is one of the major fields that is transforming to a more accurate, reliable, fast, cost-effective diagnostic. CAD is currently aiding medical expert in making appropriate decision making. The history of application of CAD technology can be traced back to 1960s. However, it wasn't until the 1980s when this technology started gaining ground due to the fundamental change in the approach on the use of computer output from automated computer diagnosis to CAD [8-9].

4.1. Artificial Intelligence and Machine Learning

The concept of AI is dated back to 19th century when it started as a theory. The field has now exploded into different disciplines ranging from marketing, business and finance, advertisement, smart devices, agriculture to medical care. The transformation in the field of data storage and data analytics is driven the field and transforming our daily lives [53-54]. AI and ML are used interchangeably and there are several misconceptions about the exact meaning of each concept. AI intelligence revolves around the use of computer to mimic human cognitive functions such as learning and problem solving or decision making. In other words, AI is the application of computer program that enables machine to perform specific tasks [53].

The concept of ML revolves around the use of algorithms whose performance improve as a result of exposure to large amount of data over time. In ML, series of algorithms are applied to allow computer learn, analyze data and make decisions based on the learned knowledge. ML models are either use for classification, regression, clustering. An example of traditional ML models uses for classification include SVM and Naive Bayes classifier. Clustering ML models include K-means and tree-based clustering while Linear regression, Random Forest, KNN models are used for regression models [55-56]. ML models require large amount of data in other to make appropriate decision. Just like the way cars are driven by fuels, ML models are driven by large amount of data. Some of the application of ML can be found in IT applications, weather forecasting, Gaming, robotics, stockbroking etc [54].

ML models learn through process known as gradient descent or loss function where models minimize errors between predictive value and actual or ground truth value. After every iteration, the models compare the actual value with the objective or predictive value and adjust parameters so that the error will become smaller [57]. ML algorithms can be classified into Supervised Machine Learning (SML) Unsupervised Machine Learning (UML) and Reinforcement Machine Learning (RML) [58].

4.1.1 Supervised Machine Learning

Supervised Machine Learning SML is a branch under ML where computer algorithms are trained using labelled data. The ML models are trained using backpropagation until it can detect underlying patterns and relationship between the input data and the labelled output. The model is subsequently evaluated using test sets (unseen or untrained datasets) [59]. SML has shown to achieved high performance, however, one of the challenges associated with this type of ML is "Overfitting" where models perform very well on training set and perform poorly on test sets. Thus, scientists proposed several ways to counter this issue through cross validation, data augmentation, regularization, the use of ensemble models etc. [57, 60].

There are several applications of SML which include classification and regression tasks. Several studies have reported the application of classification algorithms for detection of clinical diseases [55-56]. SML models can be used to classify diseases into binary cases (disease/healthy, positive/ negative, findings/no findings etc.) ternary and quaternary classification in the case of different grades of tumors etc. [61]. Regression models on the other hand produces numerical correlation between the input data and output data [56]. Several prediction models are use in healthcare settings for the prediction of disease and drug discovery [61].

4.1.2 Unsupervised Machine Learning

Unsupervised Machine Learning USML is sub branch of ML where algorithms are trained using un unclassified or unlabeled dataset. Unlike SML where data are labelled and models optimized predicted value and actual value, USML learn to patterns in data and grouped them or cluster them together. USML algorithms are trained using unsorted data where models sort out the data based on similarities and differences. Another difference and limitation of USML is that they are can be unpredictable compare to SML. Some of the advantages of USML include less costly, faster, easier (which are associated with less manual work in labelling data) the use of real-time data etc. [58, 62].

Clustering algorithms are the most common USML algorithms use clustering unstructured and unsorted data into different groups. Some of the classification of clustering algorithms include hierarchal, overlapping exclusive and probabilistic algorithms. Common examples of clustering algorithms include K-means clustering, Gaussian Mixture models, Principal Component Analysis (PCA) [56, 63]. USML are currently applied in healthcare settings for classification, segmentation and medical image detection, detection of anomalies in medical data, health index monitoring, drug discovery, genomics etc. [55, 64].

4.2 Deep learning

Deep learning is a subfield of ML which is inspired by how human brain's function due to connections or synopsis of nerve cells or neurons. DL is a sub- field of ML which

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revolves around the use of multiple perceptron where each layer of the network is connected to another layer. Just like ML, DL models learn from vast amount of data which is crucial for high performance in terms of accuracy [65-66].

One of the advantages of DL over ML models (known as flat models) such as decision trees, logistic regression, SVM, etc. is that DL models can take raw input in the form of images, texts without the need of preprocessing steps. Example of DL applications include Google translation, chatbots, self-driving cars, Netflix movie suggestions, personal Assistant such as Siri and Alexa [65, 67]. The current booming of Big Data is transforming DL models who are powered by massive amount of data. Another advantage of DL models over traditional ML models is that DL models tend to result in higher accuracy with increase in the amount of training and testing datasets while ML can become saturated and stop improving [66].

4.3. Internet of Medical Things (IoMT)

IoMT also known as IoT of healthcare revolves around the internet-connection of medical appliances, hardware and software. The system enables the wireless connection between devices and server as well as storage of medical data in the cloud and subsequent analysis using AI-powered models. The application of IoMT is growing exponentially due to advancement in hardware and software engineering [17-19].

The application of IoMT include In-hospital, In-home and on-body. In-hospital IoMT revolves around the use of sensors to track patient, transmission of medical data from one department to another or between hospital devices and physicians [68]. In-home IoMT revolves around the transfer of medical data between users and primary care providers stationed in healthcare settings. An example of In-home IoMT is the remote patient monitoring where medical devises transmit medical data such as heart rate, blood pressure, blood oxygen saturation to physicians for evaluation and decision making. While On-body IoMT revolves around the use of wearable devices and implantable-IoT enable devices connected with remote tracking system or monitoring system. Despite the wide application and potential of IoMT it is limited by several challenges [69]. Some of these challenges include privacy concern, safety and security [18, 19, 68].

5. Diagnostic Imaging

Diagnostic imaging is the field under medical diagnostic that allow medical technologies and radiologists to view interior of the human body and to analyze the presence of injury or other health conditions. This type of diagnostics uses several types of machines which allow the reconstruction of structures inside the body. Some of these devices include MRIs, CT scans, X-rays, Ultrasound, mammography, arthrogram, bone density scan [69].

5.1 Radiographic Imaging of COVID-19

The field of medical imaging has transformed from conventional imaging such as X-ray, CT scan, MRI, ultrasound imaging to nuclear imaging based on PET, SPECT and hybrid imaging such as PET/CT, PET/MRI, SPECT/PET, SPECT/MRI etc. [8, 69]. Medical imaging revolves around the application of different imaging modalities to help physicians diagnose several conditions affecting patients. The use of medical imaging devices allows medical experts to view internal organs and tissue and confer diagnostics such as fracture, dislocation, cancer, pneumonia, tuberculosis etc. [69-70]. Detection of pneumonia using X-ray images and CT scan machines have become an alternative or confirmatory test for detection of non-COVID-19 (such as bacterial and influenza viral pneumonia) and COVID-19 [15].

X-ray imaging is one of the most common techniques use in clinical and other healthcare settings for diagnosis of wide range of diseases. One of the advantages of X-ray imaging over other imaging techniques include low radiation, availability (i.e., due to

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high demand), low cost, moderate sensitivity and low radiation dose [71]. The classification of chest X-ray images by Radiologists include posteroanterior, anteroposterior and lateral view as shown in Figure 4. These classifications are based on the position and orientation of patient parallel to the X-ray source and detector panel. Side view or lateral view differs from both anteroposterior and posteroanterior (which are known as frontal views). Side view is obtained as a result of the combination of posteroanterior view and projection of the x-ray from one side of the patient to the other or right to left. The frontal views are based on the positioning of the X-ray source to the front or rear of the patient where posteroanterior X-ray imaging is generated in erect standing position of the patients while anteroposterior X-ray image is obtained from patients in the spine position [71-72].

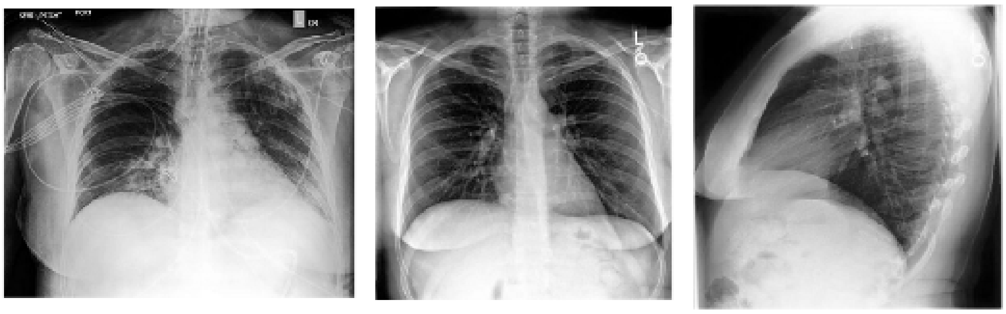

Figure 4. Left: Anterior-posterior (AP) view chest X-ray. Middle. posterior-anterior (PA) view frontal chest X-ray. Right: lateral chest X-ray

5.2 AI-Powered Detection of COVID-19 from Radiographic Imaging

Since the first declaration of COVID-19 as global pandemic by the world health organization, scientists all over the world have contributed immensely to the detection and prediction of the disease using AI-driven models. Computer aided diagnosis of covid-19 is limited to the use of X-ray and CT scan images of patients suspected with the diseases. Several AI-driven models have been deployed which include the use of models developed from scratch, pretrained models, hybrid models, ensembled models etc. [15].

The literature is copious with several studies on the use of AI-driven models for the classification of COVID-19. Some of these studies conducted binary (2-way), ternary (3-way) and quaternary classifications or combinations of more than 2 classifications. Considering the fact that there are several studies that conducted binary, ternary and quaternary classifications in one article, this study will attempt to categorize these studies based on the highest number of classifications.

5.2.1 AI-Powered Detection of COVID-19 from X-ray images

A) Binary

The study conducted by Gayathri et al. [73] applied several pretrained networks and their combinations for detection of COVID-19 from X-ray images. The detection process revolves around the use of pretrained networks for future extraction, the use of sparse autoencoder for dimensionality reduction and subsequent use of Feed-Forward Neural Network for classification of COVID-19 from non-COVID-19 images. The models are trained and tested using 1046 (504 COVID-19 and 542 non-COVID-19) images obtained from 2 public accessible datasets. The performance evaluation of the models has placed the combination of InceptionResNetV2 as the best performing model with 0.9578 accuracy and 0.9821 AUC.

The study conducted by Nayak et al. [74] proposed an automated detection of COVID-19 from X-ray images. The study evaluated 8 TL models which include ResNet34, ResNet-50, MobileNet. InceptionV3, SqueezeNet, AlexNet, VGG16 and GoogleNet for binary classification of COVID-19 and normal cases. The models are trained and tested using dataset obtain from public domains which include dataset prepared by JP Cohen,

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Covid-chest-X-ray and ChestX-ray8 dataset with a total of 703 (500 normal and 203 COVID-19 images). In order to help expand the number of training images, data augmentation techniques were implemented which include flipping, rotation, scaling and Gaussian noise. The comparison between model performances has shown that ResNet34 achieve the highest accuracy with 98.33%, precision of 96.77%, specificity of 96.67%, 0.9836 AUC and 0.9836 F1-score.

Another study that utilized several pretrained models is provided by Narin et al. [75]. The study applied 5 TL models which include InceptionV3, Inception-ResNetV2, ResNet50, ResNet101 and ResNet152. The study conducted several binary classifications which include COVID-19 vs healthy cases, COVID-19 vs viral pneumonia and COVID-19 vs bacterial pneumonia using several datasets curated from public accessible domains. The comparison between model performances revealed that ResNet50 achieved the best results with 96.1% accuracy on the first dataset, 99.5% on the second dataset and 99.7% on the third dataset.

The use of CAD of COVID-19 from X-ray images is proposed by Naseer et al. [76]. The study applied 2 networks which include Artificial neural network (ANN) and Artificial Recurrent Neural Network (Long-Short Term Memory (LSTM)) network. In order to maximize the number of training data, the study conducted several data augmentation process which include image enhancement, color transformation, geometric transformation and noise injection which yielded 3220 images. Training of the models revolves around 3 phases which include training using raw CXR images, training using pre-processed images and training using enhanced images. The classification process relies on the use of CNN as feature extractor which is fed into the LSTM network for classifications. The performance evaluation outcome of the joined CNN-LSTM model yielded 99.02% accuracy, 100% sensitivity and 99% specificity.

B) Ternary

The binary and ternary classification of X-ray images of COVID-19, non-COVID-19 and viral pneumonia using pretrained model is proposed by Aziz et al. [77]. The detection process follows the use of connected layer of ResNetV50V2 model for feature extraction, the use of reduction methods for reduction of feature dimension and the use Gaussian SVM for classifications. The TL models is trained and tested using dataset acquired from Cohen and Morrison, 2020 with 874 images (254 COVID-19, 310 non-COVID-19 and 310 viral pneumonia. In order to increase the number of training set, data augmentation was conducted via flipping, rotation, shearing, height and weight shift. The result of the model performance evaluation yielded 99.5% accuracy for binary classification and 95.5% for ternary classifications.

The ternary classification of X-ray images using a DL model known as CVDNet is proposed by Ouchicha et al. [78]. The model is designed based on residual neural network which is constructed using 2 parallel levels with different filter sizes in order to capture both global and local features of the input datasets. The study trained and validated the model using dataset downloaded from online repositories which include viral pneumonia (1345), COVID-19 pneumonia (219) and normal cases (1341). The performance evaluation of CVDNet based on 5k-fold cross validation resulted in an average accuracy of 96.69%, 96.84% recall, 96.72% precision and 96.68% F1-score for 3-way classification.

The use of CNN-based DL fusion framework for the ternary classification of COVID-19 and non-COVID-19 cases is proposed by Shorfuzamman et al. [79]. The study transfer weight (parameters) of 3 TL models which include VGG16, ResNet50V2 and GoogleNet (InceptionV3) which are combined into a single model in order to extract image and classify the images using custom classifier and the subsequent use of gradient-weighted class activation mapping in order to view the infected zones. Apart from the use of model performance metric evaluations, the study also conducted cross validation which result in average performances of the model on 1848 image datasets obtained from open domains (Cohen et al with 616 COVID-19 and Money 2018 with 616 non-COVID-19 viral pneumonia and 616 healthy cases). ResNet50V2 as the best performing model achieved an overall

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accuracy of 95.49%, 99.19% sensitivity, 98.27 specificity and 95.94% AUC. Workflow of the proposed system is illustrated in Figure 5.

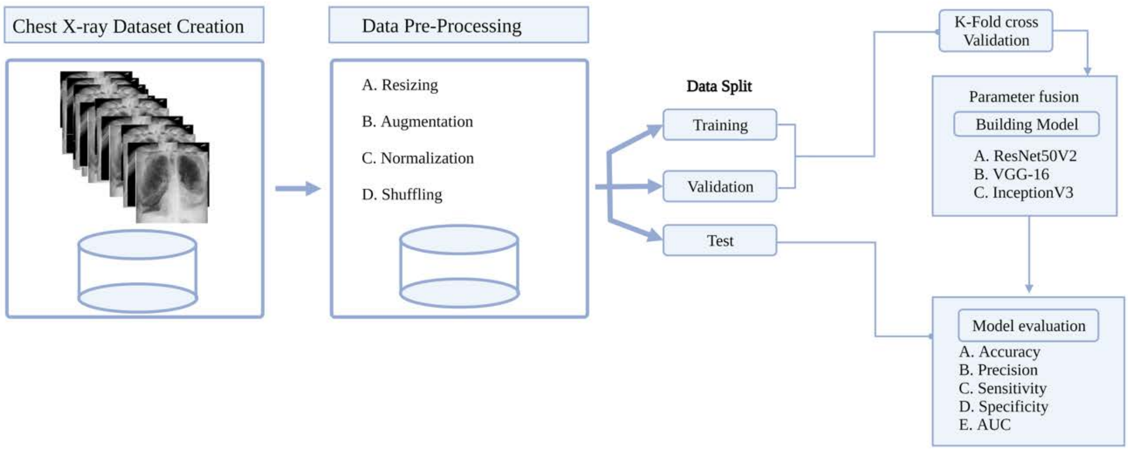

Figure 5. AI-powered Detection of COVID-19 from X-ray images

C) Quaternary

The study conducted by Li et al. [80] applied Cov-Net model for the 3-way and 4-way classification of COVID-19, non-COVID-19 viral pneumonia and lung opacities acquired from 2 public accessible dataset. The first dataset contains 3 categories named as D1 while the second dataset contain for classes named as D2. One of the variations of this technique over current techniques is the use of residual network along with asymmetric convolution and attention mechanism embedded as the backbone for feature extractor and the subsequent application of skip-connected dilated convolution with carrying dilation rates in order to attain sufficient feature fusion among low-level detail and high-level semantic information. The performance of the model on the 2 datasets resulted in 0.9966 and 0,9901 accuracies respectively.

The study conducted by Ibrahim et al. [15] applied pretrained AlexNet model for several binary classifications, ternary classifications and quaternary classification of X-ray images of COVID-19, viral pneumonia, bacterial pneumonia and normal cases. The TL model is trained and tested using several datasets curated from online sources. The result of the 4-way classification of X-ray images using pretrained AlexNet resulted the model achieved an accuracy of 93.42%, sensitivity of 89.18%, and specificity of 98.92%.

Hira et al. [81] applied DL for the binary and multiclass prediction of COVID-19 from X-ray images. The study applied 9 DL models which include AlexNet, Se-ResNet50, ResNeXt-50, Se-ResNeXt-50, ResNet-50, InceptionResNetV2, InceptionV4, GoogleNet and DenseNet121. The models are trained and validated using several datasets curated from open sources. The performance evaluation of the 9 models has shown that Se-ResNeXt-50 achieved the best performance for 3-way classification with 97.55% accuracy and 96.89% for 4-way classifications.

5.2.2 AI-Powered Detection of COVID-19 from CT scans

The classification of COVID-19 from non-COVID CT scan images using AI-based CAD is proposed by Syed et al. [82]. Detection of COVID-19 from non-COVID-19 was conducted via 4 stages which include curations of CT scans images from 2 public accessible repositories which include SARS-COV2-CT (1229 non-COVID-19 and 1252 COVID-19) and Community acquired pneumonia (1500 CT images) modification of 3 pretrained s networks which include ResNet50, ResNet101 and VGGNet16, selection of activation

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function and enhancing firefly algorithms for feature selection and finally the use of descending order serial approach for fusing optimal selected features and classification using supervised ML such as SVM classifier. The outcome of the model evaluation has yield 97.9% accuracy, 97.63% recall and 97.63% precision and approximately 34 seconds' computational time.

The study proposed by Chaddad et al. [83] applied DL-TL for the prediction of COVID-19-19 from CT scan images. The study applied 6 DL architectures which include AlexNet, DarkNet, DenseNet, GoogleNet, NasNet-mobile and ResNet18. The models are fed with (1) raw datasets and (2) region of interests corresponding to ground glass opacities, pleural effusion and consolidation of 100 lung CT images generated from 60 COVID-19 patients. The comparison evaluation of the model performances has shown that DarkNet achieved the best result with an AUC of 88.16% and accuracy of 82% on raw dataset and an AUC of 90.20% and accuracy of 82.30% after incorporating 3 additional ROIs.

The binary and ternary classification of COVID-19 from CT scan images using 2 pretrained models is proposed by Mishra et al. [84]. The study applied pretrained VGG16 and ResNet to classify non-COVID-19 pneumonia, COVID-19 pneumonia and normal cases (400 each in order to achieve class-balanced). The study also conducted data augmentation in order to increase the number of training set and fine tuning the model to optimize it performance. The model is evaluated on the basis of stratified 5k cross validation and the performance shows that both models achieve more than 99% accuracy for binary classification, while VGG16 achieved 86.74% accuracy and ResNet achieved 88.52% accuracy for ternary classifications.

The study conducted by Katar and Dumman [85] developed a CNN which consists of 19 layers for binary classification of COVID-19 and normal cases from CT scan images. The model is trained (using 1600 images of both positive and negative cases) and tested (using 400 of both positive and negative cases). The performance evaluation of the model resulted in 97.5% accuracy. The study conducted by Kogilavani et al. [86] applied several DL models for binary classification of COVID-19 and normal cases. The study curated 3873 CT (1958 positive cases and 1915 negative cases) scan images which are partitioned into 70% for training, 15% for testing and 15% for validation. The images are trained and evaluated using DenseNet-121, EfficientNet, MobileNet, NASNet, Xception and VGG16. The comparison of the model performances has shown that VGG16 achieve the best result with 97.68%.

The application of pretrained model (modified based on random, Bit-S and Bit-M) for the detection of COVID-19 from over 190 thousand CT scan images collected from 4 thousand patients is proposed by Zhao et al. [87]. The study revolves around the use of pretrained ResNet-V2 (group normalization was replaced with batch normalization and weight standardization for all the convolutional layers) for the classification of COVIDx-CT-2A images into normal and control cases. The evaluation of the model performance resulted in 97.9%, 98.8% and 99.2% accuracy for Random, Bit-S and Bit-M respectively.

The application of 2D DL approach for the classification of COVID-19 and non-COVID-19 from CT scans images are proposed by Ko et al. [88]. The model termed as Fast-Track COVID-19 Classification Network (FCONet) was designed using either one of the pretrained networks (Xception inception-V3, ResNet-59 and VGG-16). The designed model was trained using 3993 total images acquired from Wonkwang University Hospital, Chonnam National University and Italian Society of Medical and Interventional Radiology public database. Evaluation of the model performance has shown that FCONet-ResNet-50 achieved the best result with 99.87% accuracy, 99.58% sensitivity and 100% specificity.

5.2.3 IoT-enabled Devices for Detection of COVID-19

Iskanderani et al. [89] 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

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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. [90] 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. [91] 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. [92]. The X-ray images are collected using medical sensors followed by detection using Faster Region CNN (FR-CNN) and ResNet101 as the backbone network.

Rehman et al. [93] proposed real-time detection of COVID-19 from X-ray images. The framework is developed based on CNN-residual neural network (ResNet-50). The mechanism behind the real-time CAD revolves around the upload of X-ray images from healthcare centers and remote clinics and subsequent classification using ResNet-50. The performance of the proposed IoT/CAD system achieved 98% accuracy and 0.975 AUC on chest X-ray images acquired from online repositories (already augmented and contains 1824 total images where 912 are non-COVID-19 and 912 COVID-19 cases).

Punitha et al. [94] proposed a novel e-healthcare platform for diagnosis of COVID-19 using optimization algorithm. The framework is designed based on the classification approach for the detection of abnormalities in lung CT images via Whale Optimization Algorithms (WOA) optimized Wavelet Neural Network (WNN). The mechanism behind e-healthcare system revolves around the extraction of the Laws 16 texture energy measures from the preprocessed CT lung images and subsequent classification using WNN classifier. Evaluation of the proposed system on public accessible datasets resulted in 84.8% accuracy, 82.0% sensitivity and 73.3% specificity for binary classification of COVID-19 and non-COVID-19 cases.

6. Open Research Issue

The increase generation of medical data in the healthcare settings has contributed to the development of high-performance models' tasks with identifying patterns, extracting features, prediction and classification of medical data [65, 67]. Analysing high amount of dataset generated in medical settings require the use of reliable, fast and accurate system which can relieve the workload of medical data analyst. The application ML models over the last decade has shown to addressed this issue. Several ML models are use in healthcare settings as a form of CAD to assist physician in accurate diagnosis and appropriate decision making [61, 66].

Despite the wide application of ML models in healthcare settings, they are hindered bus several challenges which include lack of sufficient amount of data. Training of ML models using substantial amount of data is crucial for high performance. In order to address the shortage of dataset, scientists developed TL where weights and features are extracted from trained models and repurpose on new task with insufficient datasets. The use of TL models also known as pretrained models have shown to outperformed models developed from scratch [95-96]

Another challenge facing the application of ML models is underfitting and overfitting. Underfitting occur when ML models perform poorly on both training and testing set (I.e., when models neither perform well on training dataset nor generalize new or unseen dataset). Underfitting is associated with high bias and low variance While overfitting occur when machine learning performs well on training datasets but perform poorly on test sets [60, 97]. Overfitting is associated with high variance and low bias. Performance of ML models depend on type of images use [60]. Poor performance can also be related with training images with small amount of data or data that contains noise. The use of data augmentation techniques such as rotation, flipping, mirroring, zooming, cropping etc increase the number of training set [98]. Other pre-processing steps are used to remove noise from images, resize images to fit into the models and extract features that can be classified using classifier [98-99].

The landscape of AI-powered models is changing from the application of single models to hybrid of ensembled models. Ensembled models combined predictions from two or more models. Ensembled learning include parallel ensembled and Sequential ensemble methods. Ensembled learning techniques can also be classified as Bagging (such as bootstrap aggregation), boosting (gradient boosting machine or GMB, LightGBM, Adaboost etc.), stacking, and blending. The use of ensembled models have are associated with improving performance (originally developed to reduce variance thereby improving performance) and robustness [100].

7. Conclusion

The global pandemic witnessed as a result of spread of COVID-19 disease associated with SARS-CoV-2 has change the landscape of diseases diagnosis. Several techniques have been developed and repurpose in order to provide accurate and reliable detection of the virus. Molecular testing based on RT-PCR is regarded as the standard approach for detection of COVID-19 followed by antigen-based detection. Despite the high reliance on these approaches, they are limited by so many challenges which include false positive results, low accuracy, the need of trained pathologist, the need for chemical, longer processing time, high cost etc. These factors limit the use of molecular testing in remote areas and underdeveloped countries. This call for the need to provide an alternative approach that can provide accurate results, eliminate the need of toxic chemicals and high cost of assays. Thus, healthcare experts turn to medical imaging such as X-ray, CT scan and lung ultrasound as an alternative or confirmatory testing. However, this approach is also clouded by several challenges which include tediousness in the case of interpretation of large number of cases and miss-interpretation.

To address this issue scientists incorporated CAD using ML models and classifiers. These models have shown to achieved high performance compare to human interpretation. In order to allow real-time testing, scientists developed IoT/AI-enabled system or e-healthcare system which allows upload of medical images and subsequent classification of cases into binary (COVID-19 and non-COVID-19) 3-way and 4-way classification (COVID-19, non-COVID-19 viral pneumonia, bacterial pneumonia and health cases). Thus, this review provides extensive knowledge of the state-of-the-art detection of COVID-19 using molecular testing, CAD and IoT/AI-powered detection.

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