Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

CHAPTER 2

Diagnostic tools and automated decision support systems for COVID-19

Noor E. Hafsa
King Faisal University, Al Ahsa, Saudi Arabia

2.1 Introduction

Since the onset of 2020, the outbreak of COVID-19 has been causing a serious health crisis all around the world. COVID-19 as a novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)), is a new strain in the family of coronaviruses that have not been previously identified in humans [1]. Due to the very rapid transmission of COVID-19 over many territories in multiple continents, the World Health Organization (WHO) declared it as a global pandemic on March 11, 2020. As of August 23, 2020, over 23 million COVID-19 cases have been confirmed worldwide with 808,697 number of confirmed deaths, according to Worldometers report [2]. The outbreak of SARS-CoV-2 has imposed substantial pressure on healthcare systems globally. A larger number of COVID-19 cases admitted to intensive care units (ICU) suffer from respiratory distress and hypoxemia and require endotracheal intubation and ventilation treatment facilities [3]. However, in the majority of cases, hospitals are not well equipped with such expensive machines and medical facilities around the globe. Furthermore, COVID-19 has a comparatively longer incubation (1–2 weeks) period and is highly infectious, making it particularly important to identify the infected cases at early stages and to isolate the subjects from the healthy population to avoid the risk of human-to-human transmission in the community level. The widespread availability of accurate and rapid diagnostic procedures is extremely valuable in unwinding the complex dynamics associated with SARS-CoV-2 infection and immunity. Clinical laboratories, university research groups, and biotechnology companies are working diligently toward the development and production of crucially required diagnostic test kits.

Researches and Applications of Artificial Intelligence to Mitigate Pandemics
http://dx.doi.org/10.1016/B978-0-323-90959-4.00002-X
Copyright © 2021 Elsevier Inc.
All rights reserved.

COVID-19 displays a range of clinical manifestations, from mild flu-like symptoms at the early onset to life-threatening conditions at severe stages. Therefore, it is highly important to efficiently diagnose the initial stages of infection to identify and isolate COVID-19 patients from individuals with and without comorbidities. This avoids the community transmission and unnecessary quarantine of healthy individuals. Moreover, an early diagnosis allows the physicians to provide prompt medication to the patients with high risk for developing more serious complications from COVID-19 infection. The mutational variability associated with SARS-CoV-2 necessitates the development of more advanced diagnostic tests based on viral genome sequencing. This could be an essential tool to determine the rate and degree of mutational changes in viral RNA genomes and unraveling newly emerging strains of the virus for effective therapeutic development.

Currently, publicly available COVID-19 diagnostic tests can be classified into three major categories. The first category includes molecular assays for detection of SARS-CoV-2 viral RNA using reverse transcriptase–polymerase chain reaction (RT-PCR) techniques, nucleic acid hybridization or amplification strategies, and amplicon-based metagenomic sequencing methods. The second group belongs to serological and immunological assays that mostly depend on detecting antibodies in the human serum, produced by individuals previously exposed to SARS-CoV-2 virus or on the detection of antigenic proteins in the currently infected individuals [4]. The final category includes the medical imaging-based diagnosis that largely relies on identifying clinical manifestations of acute respiratory infection in radiography images, including chest X-ray, computed tomography, and lung ultrasound, of the infected individuals.

2.2 Molecular assay-based diagnosis

SARS-CoV-2, the causal virus for COVID-19, is a single-stranded positive-sense RNA. On January 10, 2020, the entire genome sequence for SARS-CoV-2 was published for a rapid demand for developing diagnostic kits for the detection of viral genomes in affected individuals. The accessibility to the viral sequence data greatly facilitated the design of primers and probes for SARS-CoV-2-specific genomic DNA detection and amplification [3]. Reverse transcriptase–polymerase chain reaction is one of the principal molecular assay techniques for viral nucleic acid detection.

2.2.1 Reverse transcriptase polymerase chain reaction

RTP-PCR is a molecular diagnostic assay for the detection of SARS-CoV-2 viral RNA. In the case of acute respiratory infection diagnosis, the RT-PCR is routinely utilized for the detection of causal viruses from respiratory secretions [4] and is considered as the gold standard for the identification of SARS-CoV-2 virus. At present, RT-PCR assay for COVID-19 diagnosis generally relies on the nasopharyngeal and throat swab-based specimens collected from the upper respiratory tract. Additionally, the viral RNA was reported to be found in serum, saliva, stool, and ocular secretions in a few RT-PCR-based diagnostic studies [5–8]. The majority of the molecular diagnostic testing uses real-time RT-PCR technology that targets different SARS-CoV-2 genomic regions. Specifically, 90% of the currently available molecular assays for SARS-CoV-2 detection utilize RT-PCR technologies [4].

2.2.2 RT-PCR assay procedure

The RT-PCR is a variation of a standard polymerase chain reaction that involves the amplification of specific viral genetic material obtained from small samples. The assay begins with the laboratory conversion of SARS-CoV-2 into complementary DNA (cDNA) strands using RNA-dependent DNA polymerase, which is also known as reverse transcriptase (RT). The RT relies on small DNA sequence primers designed to specifically bind complementary sequences in the viral RNA genome and the DNA polymerase enzyme to generate a short cDNA copy of the viral RNA. RT-PCR technique consists of two steps: (1) SARS-CoV-2-specific genome detection and (2) amplification. In real-time RT-PCR, the amplification can be monitored in real-time with the progression of the PCR, using either a fluorescent dye or a sequence-specific fluorescent-labeled DNA probe. The amplification process is repeated for about 40 cycles using an automated procedure until a fluorescent or an electric signal detects the viral cDNA, indicating the presence of SARS-CoV-2 in the sample [8]. An illustration of the RT-PCR assay procedure is shown in Fig. 2.1.

2.2.3 Diagnostic precision of RT-PCR-based diagnosis

The real-time RT-PCR, in general, is sensitive (i.e., the ability to accurately identify the patients with the disease) and a specific (i.e., the ability to accurately identify the patients without the disease) diagnostic procedure for COVID-19. A recent systematic review-based meta-analysis on 16 studies

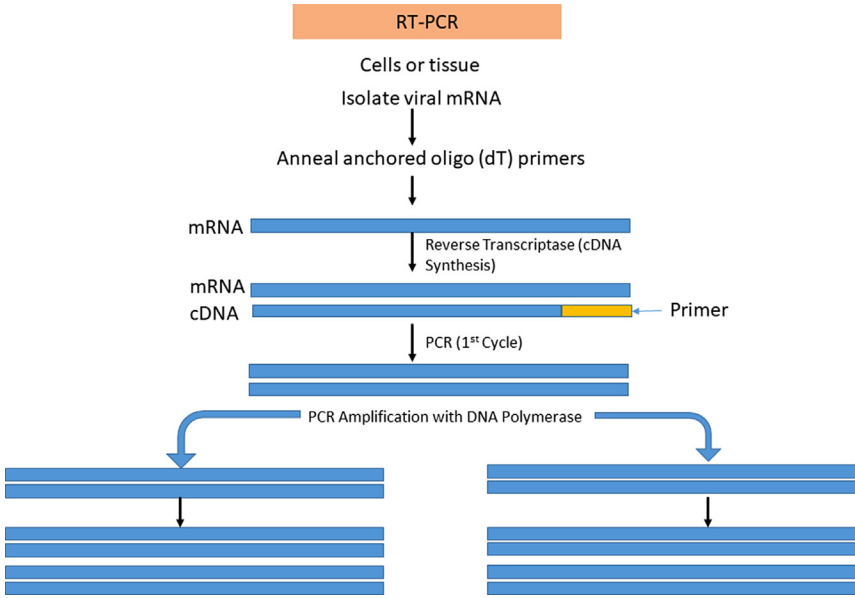

Figure 2.1 Reverse transcription–polymerase chain reaction (RT-PCR) mechanism explained. The reverse transcriptase generates cDNA copy of the specific segments of SARS-CoV-2 viral mRNA, which is then multiplied by multiple cycles of PCR amplification with DNA polymerase. *Reproduced and modified the image from [9].*

showed that RT-PCR with sputum sample provided the highest sensitivity (97.2% [90%(min)–99.7%(max)]) among all other available testing methods for COVID-19 diagnosis, including clinical (computed tomography) and immunological (IgM and IgG antibodies) testing [10]. Additionally, in this study, the authors reported the meta-analysis results of RT-PCR diagnostic tests using different types of samples, including rectal stool/swab, urine, plasma, saliva, nasopharyngeal aspirate/swab, and throat swab. Of all these samples, RT-PCR results with the respiratory samples demonstrate higher sensitivities when compared to clinical samples in the sensitivity analyses. Concerning the specificity parameter, no statistical meta-analysis result was reported due to the scarcity of RT-PCR studies involving control groups. The computed tomography-based testing turned out to be the second most sensitive method by the meta-analysis presented in the study, followed by the immunological antibody testing as the third-highest sensitive assay.

2.2.4 Limitations of RT-PCR-based diagnosis

Although RT-PCR is considered as the golden-standard diagnostic test and is reported to be the most sensitive method for diagnosing COVID-19, it

is hardly without any downside. The main limitation associated with the RT-PCR test is the risk of eliciting false-positive and false-negative results. RT-PCR test may yield false-negative results if there is a viral genome insufficiency in the sample or non-amplification of viral genomes during the PCR reaction [10]. Furthermore, several "suspected" cases were reported in a study by Wang et al. (2020), in which discrepancies were observed between typical clinical COVID-19 characteristics (with identical findings in computed tomography) and RT-PCR test results [11]. Hence, a negative RT-PCR outcome does not exclude the possibility of COVID-19 in all cases and should not be used as the sole criterion for making critical decisions related to treatment and patient care management. Other notable disadvantages are (1) the RT-PCR process requires expensive laboratory instrumentation; (2) highly skilled health technicians; and (3) it is time consuming and can even take several days to generate results [12].

2.2.5 Conclusion

RT-PCR is the most definitive diagnostic method for the detection of the SARS-CoV-2 virus, which demonstrates high accuracy for the identification of true positive infections. However, in the case of dubious RT-PCR results under typical clinical manifestations, the clinical features, such as computed tomography diagnosis, could be combined to achieve a more reliable diagnostic decision. Biotechnological companies and laboratories worldwide are striving to accelerate the molecular assay procedure and develop various other alternative assay techniques to further improve the diagnostic efficiency of the molecular assays.

2.3 Serological and immunological assay-based diagnosis

Serology, in general, is a diagnostic examination procedure involving blood serum, concerning immune system's response to pathogens or introduced substances. In the case of COVID-19, the serologic test is primarily designed to detect antibodies produced in serum or plasma components of blood in response to SARS-CoV-2 spike protein. The finding of the presence of antibodies in serum often indicates an immune system response to an antigen (SARS-CoV-2 virus) from recent exposure to the disease or the foreign protein. As antibodies are specific proteins made by the immune system in response to infection, they can be detected in the blood of people who are tested after infection, indicating an immune response to the infection. Furthermore, antibody test results can be important for identifying

previous infections in mild or asymptomatic people [11,13]. Antibodies, also known as immunoglobulins, are specialized proteins with a form of Y-shape that can recognize antigen proteins located on microbial surfaces as foreign particles [4]. Among the antibodies that are specific to the SARS-CoV-2 virus, IgM and IgG are the most notable ones. IgM appears first in response to a SARS-CoV-2-specific antigen implying an inception stage of the infection. On the other hand, IgG antibodies have a higher affinity for the target antigen and are more specifically able to bind the substance which triggers the immune response. This type of antibody is generated later in the course of infection and plays a key role in establishing a postinfection community [4,14]. The principle of COVID-19 serology testing is based on targeted antibodies binding to SARS-CoV-2-specific antigens. The collected blood serum is first applied to a testing platform containing copies of viral antigen. The capillary action draws the blood through the testing device where it mixes with the antigens. If antibodies are developed in the patient's blood against SARS-CoV-2, they will recognize and bind to the corresponding antigens, indicating previous exposure to SARS-CoV-2.

2.3.1 Types of serology-based testing

Serology-based tests, as a rapid and a point-of-care test, detect the presence of patient-generated antibodies against the SARS-CoV-2 virus that causes the disease COVID-19. Several platforms for the COVID-19 serology test are available in the market including enzyme-linked immunosorbent assay (ELISA), lateral flow immunoassay (LFIA), and chemiluminescent immunoassay (CLIA) [4]. These immunoassay procedures can quantitatively or qualitatively detect SARS-CoV-2 specific antibody isotypes, such as IgM and IgG in human serum, plasma, or whole blood in vitro.

The test principles of ELISA, LFIA, and CLIA assays are briefly described in the subsequent paragraphs based on relevant literature.

ELISA: ELISA is one of the most common assay techniques for quantitative and qualitative measurement of the human anti-COVID-19 antibody in serum. The procedure utilizes a microplate-based enzyme immunoassay technique and the time required to produce the result is typically 1–5 h. In the case of SARS-CoV-2, the microplate is coated with viral protein. If the specific antiviral antibodies are present in the tested specimen, that will bind the antigen specifically, and the bound antibody–protein complex can be detected using an additional tracer antibody producing a colorimetric or fluorescent-based readout, proportional to the amount of the level of antibodies present in the sample. ELISA is designed to test multiple samples

at a time and can be adapted to the increased throughput automation as a point-of-care diagnostic tool [14].

LFIA: LFIA is a chromatographic assay-based test that qualitatively assesses the presence of an antibody from a patient's sample or specimen. The test device is small, portable, and can be used at the point-of-care. LFIA is considered as a rapid diagnostic test (RDT) as the typical time to obtain the result is 10–30 min. When the serum fluid is applied to a substrate material, the lateral capillary flow allows the sample to flow over a membrane of immobilized-coated SARS-CoV-2 antigen. If the specimen contains the anti-CoV antibodies, that are collected at the membrane line. Along with cocollected tracer antibodies, a colored line is visualized in either IgM or IgG antibody region to indicate the results. If the specimen does not contain SARS-CoV-2 antibodies, no colored test band will appear, indicating a negative result. The LFIA is inexpensive with no requirement of trained personnel. One of the drawbacks is that it provides only qualitative (positive or negative) results. A diagnosis of infection may become more feasible when the assay result is used in conjunction with other symptoms [14].

CLIA: CLIA is an assay procedure that combines the chemiluminescence technique with immunochemical reactions. Like other labeled immunoassays, such as ELISA, CLIA also uses chemical probes that generate light emission for labeling the antibody [12]. Recently, Cai et al. (2020) proposed a peptide based magnetic chemiluminescence enzyme immunoassay technique for serological diagnosis of COVID-19 [15]. At a commercial level, Diazyme Laboratories, Inc. (San Diego, CA) introduced two serological tests for SARS-CoV-2 that can be run on the fully automated Diazyme DZ-lite 3000 plus chemiluminescence analyzer [16].

2.3.2 Diagnostic precision of serology-based testing

Several researches were undergone to analyze the diagnostic accuracy of serological testing of COVID-19 [17–20]. De Moura et al. conducted a structured systematic review and meta-analysis to statistically evaluate the diagnostic characteristics of serology-based COVID-19 testing [17]. Five available studies (IgM and IgG-antibody test results with rRT-PCR diagnostic reference standards) were extracted from the literature to assess the accuracy, sensitivity, specificity, and other relevant evaluation metrics for serology-based tests for COVID-19 diagnosis. The meta-analysis in this study demonstrated suboptimal performances (in terms of pooled sensitivity and specificity) of IgM and IgG antibody-based diagnostic testing for SARS-CoV-2 and argued about the adequacy of serology-based testing

to confront the challenges posed by COVID-19. In another meta-analysis study by Bastos et al., the sensitivity and specificity were analyzed based on 40 literature studies, stratified by serological testing methods (ELISA, CLIA, and LFIA) and immunoglobulin class (IgG, IgM, or both) [18]. In this systematic meta-analysis study, the pooled sensitivity for CLIAs found to be highest (97.8%), followed by ELISAs (84.3%), and LFIAs (66.0%). The study undermines the potentiality of LFIAs as a rapid point-of-care test by demonstrating a lower pooled sensitivity of commercial kits than the noncommercial tests. Another important finding in this study is that the serology-based testing is found to have a significantly higher sensitivity at the later stage of the disease compared to the initial phase. Freeman et al. conducted a study describing the optimization and validation of a SARS-CoV-2 spike protein ELISA using receiver operating curve (ROC)-based specificity and sensitivity analyses [19]. The study reported an ELISA-based serologic testing method that showed more than 99% of specificity and a sensitivity of 96%, with the recommendation of using the assay in identifying prior SARS-CoV-2 infections without molecular diagnostic information. At the commercial-level research, ACROBiosystems, a target therapeutic manufacturing company, analyzed nine commercial SARS-CoV-2 ELISA immunoassay kits and reported the sensitivities (93%, 93%, and 67%) and specificities (100%, 93%, and 96%) for a total antibody, IgA and IgG antibody testing, respectively [20].

2.3.3 Uses of laboratory-based assays in the context of AI and data science

Generally, laboratory-based assays serve as reference standard to assess other alternative assay techniques for COVID-19 diagnosis. Especially, RT-PCR-based molecular assay is widely used as a gold standard reference for evaluating diagnostic performances of all other testing methods, including immunological assays and clinical feature-based assays. "AI-assisted diagnostic" also utilizes the RT-PCR results (COVID-19 positive or negative) as ground truth labels for patient classifications. From data science perspective, quantitative immunological assay data could be important predictors for forecasting the prognosis and predicting the severity level of COVID-19.

2.3.4 Conclusion

Serology-based antibody testing can be used as a supplementary tool for diagnostic, public health, and epidemiological surveillances. While molecular testing provides the gold standard for identifying viremia cases, the

serological detection of SARS-CoV-2 specific antibodies can contribute to increase the true positive case counts and in identifying the asymptomatic infections. As a rapid and a point-of-care method, the antibody testing may assist with precision diagnoses as well as characterization of the spread and prevalence of the disease.

2.4 Chest and lung imaging-based diagnosis

Until this point, COVID-19 diagnosis is predominantly conducted by the viral nucleic acid detection technique called RT-PCR. However, lower diagnostic precision, unavailability of adequate sampling kits due to high demands, and time-consuming assay procedure are making the RT-PCR less favorable in the current clinical practices.

On the contrary, the medical diagnostic imaging has arisen to be promising and a feasible alternative for many decision-making processes related to COVID-19 including diagnosis, complication assessment, prognosis, and triage decisions for hospitalization, because chest imaging of COVID-19 patients typically manifest pulmonary abnormalities in most cases [21–25]. Specifically, chest radiography (CXR) and computed tomography (CT) are two imaging modalities that are being extensively employed by the forefront hospitals in outbreak sites for making clinical decisions related to COVID-19 [26–29]. Lung ultrasound is the final imaging modality, which shows potential findings of COVID-19 pneumonia in an evaluation study on the critically ill patients in China [30].

2.4.1 Chest X-ray imaging modality

Chest X-ray (CXR) imaging modality is a technique that generates static images following the passage of X-rays through the patient. The imaging technology in CXR is based on X-rays, which represent a form of ionizing electromagnetic radiation. The X-rays are captured behind the patient by an X-ray detector after passing through the body. The detector could be a film sensitive to X-rays or a digital detector [31]. The plain chest radiograph is often referred to as CXRs in the field of radiology.

2.4.2 COVID-19 diagnosis using chest X-ray

CXR-based COVID-19 diagnosis is discussed in terms of common radiographic features and radiological classification in light of COVID-19 radiology article by *Radiopaedia* [22].

Radiographic Features: CXR is typically the front-line imaging modality used for patients with suspected COVID-19. Typical CXR-based findings of COVID-19 either correspond to atypical pneumonia in a mild form, or organizing pneumonia in the form of interstitial pneumonia, characterized by lung inflammation. CXR imaging is reported to have limited sensitivity for COVID-19. Bilateral and/or multilobar involvement is commonly found in COVID-19 cases. While chest radiographs may be normal in mild or early course in the disease, the findings become extensive about 10–12 days after the beginning of symptoms [32]. The most frequent CXR findings are airspace opacities, often described as consolidation or, less frequently as, Ground-Glass Opacities (GGO). Bilateral, peripheral, and lower zone predominant distributions are often observed. On the other hand, pleural effusion is rarely observed in COVID-19 cases (only 3%) [33,34].

Radiological Classification: The CXR radiographic appearances are classified into four (4) potential COVID-19 cases, according to the British Society of Thoracic Imaging published report [34]. The COVID-19 classification and the corresponding radiographic appearances are described in Table 2.1.

2.4.3 Computer-aided diagnosis (CAD) using chest X-ray

Most frequent CXR findings for COVID-19 infected cases include GGO and air space consolidation. However, differential diagnosis from the similar CXR findings could pose a challenge for the radiologists to discriminate between COVID-19 and other types of viral and bacterial pneumonia,

Table 2.1 Plain radiography classification of COVID-19 cases and the description of corresponding radiographic appearances.

COVID-19 class	Radiographic appearances
Classic/probable COVID-19	In classic COVID-19, multiple bilateral opacities are predominantly found in the lower lobe and peripheral lung regions compared to unilateral opacities
Indeterminate for COVID-19	In indeterminate cases, the findings match with neither classic COVID-19 or non-COVID-19 descriptors
Non-COVID-19	The similar radiographic appearances as found in the case of pneumothorax, lobar pneumonia, pleural effusion(s), pulmonary edema, and/or other lung diseases
Normal	In normal cases, the radiography findings do not exclude COVID-19, rather they are correlated with RT-PCR

Source: Based on Ref. [34].

including some inflammatory pulmonary infections [23]. In many cases, radiologists with many years of experience and expertise are needed to achieve a high diagnostic precision, which also results in a relatively higher screening time. Under the current pandemic situation, this manual diagnosis is largely unproductive, undermines the efficacy of the imaging data, and carries additional risks of viral transmission. In this aspect, Artificial Intelligence (AI) could play a central role in increasing the effectiveness of the imaging tools in combating the COVID-19 outbreak. Advanced AI technologies with suitable image processing could be successfully applied to imaging data with associated clinical information for rapid COVID-19 identification, and quantifying the level of infections to assess the disease progression. The high predictive power of AI could not only expedite and automate these clinical decision processes but also could help to achieve radiologist level performances in the COVID-19 screening. Furthermore, the AI predictive models could also serve as decision support systems to guide and assist the novice radiologists in assessing the imaging data for COVID-19 detection.

A substantial amount of research was carried out on "AI-assisted diagnostic" using CXR imaging data. The efforts were consolidated mainly into the classification of CXR images into COVID-19 and other types of pneumonia exploiting different deep learning architectures. Due to the limitation of imaging data sources with the expert-labeled dataset, most methods relied on deep learning experiments in a "Transfer Learning" (TL) setting, as an alternative to training a very deep model from the scratch on a small dataset. In these works, either feature extraction or fine-tuning the network weights based on the new COVID-19 samples was used in customizing the pretrained model in the TL setup.

2.4.3.1 COVID-19 chest X-ray datasets

COVID-CHESTXRAY: Cohen et al. compiled a public dataset including pneumonia cases with CXR, specifically COVID-19 cases, along with MERS, SARS, and ARDS cases in COVID-CHESTXRAY database [35]. This database contains image data from 205 patients, and images are collected from different public sources to preserve the confidentiality of patients.

SIRM-COVID: SIRM-COVID [36] is a dataset published by the Italian Society of Medical and Interventional Radiology. The dataset includes COVID-19 cases with both CXR and computed tomography images. Only COVID-19 positive cases are included without any control group.

Furthermore, the dataset includes radiography and clinical reports for the COVID-19 cases.

COVID-19 RADIOGRAPHY DATABASE: This database is a collection of 1341 normal, 1345 viral pneumonia, and 219 COVID-19 positive CXR images, extracted from the published literature [37]. Several multinational researchers in collaboration with medical doctors developed this radiography image database. The dataset is now published in Kaggle.

BIMCV COVID-19+ Rx: BIMCV COVID-19+ is the first dataset of this kind that includes radiological findings, along with radiography images of a total of 3141 from 1311 COVID-19 positive cases [38]. Additionally, this COVID-19 database contains some images with labeled ROIs, annotated by radiologists. Until now, BIMCV COVID-19+ Rx is the largest collection of COVID-19 positive cases in terms of the number of images and patients and contains multiple samples for each patient to analyze the clinical progression of the disease. The dataset is designed to be progressive, as new images will be continuously added upon available.

2.4.3.2 Machine learning-driven image-based diagnosis

A handful of research focused on conventional machine learning (ML)-driven image-based diagnosis of COVID-19 and other related pneumonia. Pereira et al. [39] proposed a method that identifies COVID-19 in CXR images using multiclass and hierarchical classification techniques on a set of 1144 CXR images of normal, COVID-19, viral, bacterial and fungus pneumonia classes, obtained from three online repositories. As imaging features, various texture information were extracted, using both handcrafted (standard image processing) and automated (feature learning by INCEPTION-V3 deep learning model) techniques. Both texture-based and deep learned feature matrices were grouped using different combinations and resampled to feed to several multiclass (using seven labels) and hierarchical classification (using 14 label paths) schemes. The results from these classification scenarios were evaluated using F1 score. The hierarchical classification using a state-of-the-art framework was found to outperform the multiclass classification approach using five conventional ML algorithms. Elaziz et al. [40] reported an ML system for COVID-19 identification in CXR images. In this study, a set of 961 fractional multichannel exponent moments were extracted from CXR images in a parallel multicore computational framework, followed by a feature selection using differential evolution-based optimization algorithms. A K-nearest neighbour (KNN) classifier was trained on the selected features and evaluated for binary (COVID-19 positive vs

negative) classification accuracy. Another ML-based study described an extreme learning machine (ELM)-based classifier for COVID-19 identification in CXR images using public databases of CXR images [41]. A pool of features based on texture and frequency were extracted and fed to ELM learning model. A cross-validated evaluation showed a promising performance for ELM classifier, convenient for speedy training on big and diverse image datasets.

2.4.3.3 Advanced machine and deep learning techniques

Since the outbreak of COVID-19, myriads of research efforts were put to develop AI-based diagnostic and screening methods exploiting chest imaging data, for example CXR and CT. We aim to shed light on a set of literature focusing on CXR-based AI and deep learning methods for COVID-19 and other related pneumonia, in the following paragraph.

Earlier to COVID-19, a large dataset of chest radiographs was published, called CheXpert, with uncertainty labels that are associated with 14 different pulmonary diseases [42]. Later on, this large dataset facilitated many deep learning inspired CXR-based COVID-19 diagnostic studies. Using the CheXpert dataset, Pham et al. [43] described a set of convolutional neural network (CNN) models to detect the presence of 14 pulmonary abnormalities and observations that utilizes the hierarchical dependencies between diseases and uncertainty labels. Gabruseva et al. [44] proposed an automatic pneumonia detection technique using CXR images based on SSD RetinaNet with SE-ResNext101 encoder pre-trained on ImageNet. They developed a model to classify lung images into "Normal," "Lung Opacity" and "No Lung Opacity/Not Normal" using a modified RetinaNet, heavy augmentation with custom rotations and NMS thresholded postprocessing. Bansal and Sridhar [45] described a Deep TL approach using pretrained Deep CNN models to classify CXR images to detect COVID-19. Bassi and Attux [46] applied a transfer learning approach on CheXNet [47] to detect COVID-19 from CXR images. Specifically, a deep neural network model was built by using the initial weights of CheXNet, followed by a training of the network by fine-tuning the weight decay and learning rate parameters with a variable number of training epochs. Benbrahim et al. [48] in their study utilized Deep TL technique with a combination of DeepImageFeaturizer available in Apache Spark [49] and logistic regression to COVID-19 identification in CXR images. Chowdhury et al. [37] employed CNN to identify COVID-19 patients based on chest X-ray images. de Moura et al. [50] utilized a customized DenseNet161 architecture,

initialized with weights pretrained on a large image database to classify the CXR images into healthy, Pneumonia and COVID-19 cases [51]. In a study by Ghoshal and Tucker [52], the uncertainty of the deep learning prediction for COVID-19 were estimated using Bayesian CNN, that reports the a high or a low confidence score about its decision as predictive posterior distribution. The authors reported a performance improvement of the image classification via the uncertainty-aware Bayesian model and observed an increase in prediction accuracy as the model uncertainty declines. Chatterjee et al. [51] utilized an ensemble of five different pretrained deep learning models that are available, namely ResNet18, ResNet34, InceptionV3, InceptionResNetV2, and DenseNet16 to classify COVID-19, pneumonia and healthy subjects using CXR images. The interpretability of each of the models was studied using different techniques and the ResNets were found to be the most interpretable model in terms of explaining the prediction outcomes through a qualitative analysis. Khan et al. [53] proposed a CNN-based architecture, COVID-REnet, which incorporated edge and region-based dynamic features extracted from CNN with SVM classifier to classify X-ray images into COVID-19 and healthy cases. In a study by Lv et al. [54], COVID-19 and other kinds of pneumonia in chest radiography were examined using a Cascade-SEMEnet composed of SEME-ResNet50 for differentiating between bacterial and viral pneumonia, and a DenseNet169 for distinguishing between COVID-19 and other types of viral pneumonia. They introduced various components to the custom network, such as global average pooling (GAP), squeeze-excitation structure and attention mechanisms for its characteristics channel to emphasize on the pathological details of the image, U-Net segmentation of the lung regions, CLAHE for image enhancement and MoEx for rapid convergence of the network. Three pretrained Deep Transfer Learning models were investigated in a study by Narin et al. [55], in which ResNet50 model achieved the highest performance in classifying chest X-ray radiograph images. Oh et al. [56] proposed a patch-based CNN approach that can be manageable with a small number of training parameters for COVID-19 diagnosis. The proposed model consists of a segmentation network extracting lung and heart contour from the CXR images using fully convolutional DenseNet103, and a classification network to classify the chest X-ray images into four classes: normal, bacterial pneumonia, tuberculosis, and viral COVID-19 pneumonia using a Deep TL technique adapted on a base model as ResNet18. Rajaraman et al. [57] described an iteratively pruned customized CNN with a linear stack of convolutional layers, GAP, and a dense layer for COVID-19 detection in

chest X-rays. They reported that Deep Learning Ensembles combined with TL and iterative model pruning demonstrated superior performances when compared to individual models.

2.4.4 Diagnostic precision of CXR-based diagnosis

Generally, radiography imaging has shown limited sensitivity for COVID-19, as up to 18% demonstrate normal chest radiographs during the mild or early onset of the disease. However, in the case of the severe disease course, almost 97% of CXR images show clear pathological signs [32,58]. In the case of CXR-based AI-assisted diagnostic studies, several evaluation metrics are used to assess the performance of the models concerning image classification, including accuracy, sensitivity, specificity, precision, recall, area under curve (AUC), F1 score, and positive/negative predictive value. The reported accuracies of the majority deep learning-based models for COVID-19 identification ranged between 90 and 98% [42–46,48,50–57]. However, the generalizability of the models was not assessed in the majority of cases. Moreover, a detailed evaluation of AI-assisted diagnostic accuracy using CXR imaging in the case of different disease courses is not performed as yet and remains a research issue.

2.4.5 Benefits and limitations of CXR-based diagnosis

Being the front-line imaging modality, CXR accompanies some advantages, for example, CXR imaging associates with less expense, ease of carrying out, and less ionization exposure than the computed tomography (CT) scans [59]. Furthermore, the X-ray machines are much more accessible than CT scanners in the resource-constrained environment. Also, CXR imaging can be performed in the isolation rooms using portable X-ray machines, reducing the risk of viral contamination to staff, patients, and caregivers, as well as saving them time and resources required to disinfect the equipment in the radiology department [22,60]. Moreover, the automated diagnosis using chest X-rays has enabled medical practitioners to take rapid decisions.

As highlighted previously, the CXR radiograph suffers from limited precision in the early course of the disease. The radiographic evidence in the imaging should be accompanied by the molecular assay such as the RT-PCR test to get a definitive diagnostic decision.

2.4.6 Chest CT-scan imaging modality

CT refers to a computerized X-ray imaging modality that produces a detailed and high-quality images of the body using narrow beam of X-ray photons,

together with digital reconstruction. The essential components of the CT scanner are X-ray tubes and detectors. The X-ray tube produces an X-ray beam that passes through the patient, which is then captured by the detectors and is digitally reconstructed for a two- or three-dimensional image creation. Several images are digitally reconstructed from the analog data captured by the detector using various algorithms, which represent a cross-sectional slice through the patient at a certain level. Each reconstructed image is acquired at a slightly different angle and outputs from a different restoration algorithm. Constituent volume elements of the reconstructed digital image are exhibited as a two-dimensional pixel matrix, each of which transports a designation of density or attenuation, with a Hounsfield unit (HU) representation [31].

2.4.6.1 CT-scan features

In addition to common chest radiograph features, such as ground-glass opacities (GGO) and air space consolidation, CT images exhibit attributes, when present, such as consolidation with vascular enlargement, inter- and intralobular septal thickening, and air bronchogram [22]. The primary findings on adult CT scans may further include bilateral, subpleural, peripheral and basal distributed GGO, crazy paving appearances as GGOs and inter-/intralobular septal thickening, bronchovascular thickening in the lesion, traction bronchiectasis [61–67].

Among these primary chest CT findings, the peripheral distribution, ground-glass opacity, bronchovascular thickening in lesions, have been reported to demonstrate the highest discriminatory value with a *P*-value of 0.001 in a 99% confidence interval [68]. A CT scan-based classification of COVID-19 stages and the corresponding CT features are reported in Table 2.2.

Table 2.2 CT-scan based classification of COVID-19 stages and the corresponding CT features.

COVID-19 stage	CT features
Early/initial stage (0–4 days)	Normal CT or GGO only (within 2 days of symptom onset)
Progressive stage (5–8 days)	Increased GGO and crazy paving appearance
Peak stage (9–13 days)	Consolidation
Absorption stage (>14 days)	Indicating an improvement in the disease course with the appearance of "fibrous stripes", followed by the resolution of abnormalities within a month and beyond.

Source: [62,66,68].

2.4.7 COVID-19 diagnosis using chest CT scan

As CT imaging can most capture the respiratory distress syndromes that are the commonest representations of COVID-19, this is indicated for patients with moderate–severe clinical features and worsening respiratory status, and even for patients with mild clinical symptoms at the presence of risk for disease progression, according to Fleischner Society consensus statement published on 7th April 2020 [59]. Furthermore, the chest CT exams findings are used as a substitute diagnostic test in some studies [24–27,29] and they demonstrate high potential as a rapid diagnostic method of COVID-19 infection on an evaluation study of 51 RT-PCR confirmed cases [69].

According to a recent consensus statement released by the Radiological Society of North America (RSNA), the CT appearances of COVID-19 can be categorized into four classes, namely "typical," "indeterminate," "atypical," and "negative for pneumonia." In this classification system, the presence of typical CT findings is considered as a "typical" CT appearance, whereas the absence of stereotypical CT features and the presence of GGO and consolidation lacking a specific distribution are categorized as "indeterminate" appearance. An "atypical" CT appearance indicates the absence of typical or indeterminate features and the presence of other pulmonary infections such as discrete small nodules, lung cavitation, and interlobular septal thickening with pleural effusion. A "negative" scan lacks CT features suggesting pneumonia, that is the absence of GGO and consolidation. These classifications are also recommended to use for standardized reporting language [69].

2.4.8 Computer-aided diagnosis using chest CT scan

Providing that the chest CT imaging is more sensitive and indicated, recent COVID-19 radiology literature primarily focuses on the CT findings [23,24,26,28]. Several studies reported the higher sensitivity of CT findings compared to RT-PCR, and highlighted that in some incidents, the CT findings could detect the lung abnormalities in a setting of false- negative RT-PCR test [25,29].

Due to the characteristic radiological findings in CT images that can be associated with diagnostic and prognostic values for COVID-19, the "AI-assisted diagnostic" using CT-scans attained great attention among the researchers. An extensive amount of research was carried out using chest CT imaging data. Like in CXR imaging, the research efforts were focused on facilitating the COVID-19 identification using CT images through the classification of images into COVID-19 and other types of pneumonia using different AI techniques. Here, we will focus our discussion on

"AI-assisted diagnostic" using CT that relies on mainly sophisticated deep learning algorithms.

2.4.8.1 COVID-19 CT datasets

COVID-CT: This is one of the pioneer CT-scan public datasets in which images are collected from several COVID-19-related articles available online. The authors extracted the reported CT images from the portable document format (PDF) files and manually select the images with clinical findings of COVID-19 based on the image captions. The database contains 275 CT scans for COVID-19 positive cases [70].

BIMCV COVID-19+ CT: This is the CT finding of the BIMCV database. It includes 163 CT-studies, along with 2239 CT images correspond to 1311 COVID-19 positive patients [38]. This CT database shares all the features of its radiographic image-base counterpart.

Other CT Datasets: There exists a few other private datasets in the COVID-19-related literature. A nonpublic CT dataset described by Li et al. [71] contains a large number of chest CT images, including 1735 samples for community-acquired pneumonia and 1325 for nonpneumonia cases. Jin et al. [72] described another dataset comprising 877 COVID-19 positive images, along with 541 images negative corresponding to negative cases. Another private CT dataset includes 1659 COVID-19 positive images and 1027 images with community-acquired pneumonia [73].

2.4.8.2 Deep learning techniques for CT-based diagnosis

Several deep learning-based studies were conducted facilitating "AI-assisted diagnostic" using CT. Among those, a subset of research articles was selected for a brief discussion here. Mei et al. [74] described an AI system integrating chest CT findings with clinical symptoms, along with exposure history and laboratory testing that can identify the COVID-19 positive cases rapidly and accurately. The proposed system consists of three AI models, in which the first and the second models exploited CT-findings and clinical information, respectively, whereas the third model was used to combine both types of data. A set of slices were selected as "abnormal" from the full CT-scans using a set of pretrained CNN models and were fed to the second CNN model for estimating the likelihood of the presence of COVID-19. Demographic and clinical data were used to create the second ML model and finally, the combined model was constructed by integrating the output of the first two models generating the final probability for the joint model. Hu et al. [75] developed a light-weight deep learning model to distin-

guish COVID-19 from healthy cases followed by classification of images into COVID-19 and other types of pneumonia. Multiple data augmentation techniques were tested to enhance the training set used in deep-learning modeling. In another deep-learning inspired AI system, thick-section CT imaging is used to compute imaging bio-markers for a quantitative assessment of the COVID-19 associated lung abnormalities, the disease severity, and the progression under the framework of a 2.5D-based UNet structure equipped with the ResNet 34 as a backbone model (Li et al., 2020). Wang et al. (2020) utilized a collection of CT images to build a deep learning-based fully automated COVID-19 diagnostic and prognostic system. The proposed system comprised three modules, namely, automatic lung segmentation, nonlung area suppression, and COVID-19 diagnostic and prognostic analysis. A DenseNet121-FPN architecture is used for segmenting lung areas in chest CT images, followed by a nonlung area suppression operation inside the lung region-of-interest (ROI). A novel deep learning model, called COVID-19Net, pretrained on a large CT database was used to extract the lung characteristics associated with COVID-19 through TL. A recent chest CT-based study demonstrated the effectivity of "AI-assisted diagnostic" of COVID-19 on multinational datasets. The method performed both segmentation and cropping to extract the lung ROI from the CT images. Then two different techniques were applied to resample the cropped lung region and sample the multiple 3D regions for CT as input to a deep-learning algorithm producing a binary decision regarding the patient being infected by COVID-19 or not [76].

2.4.9 Diagnostic precision of CT-based diagnosis

A cohort study of 96 patients came across a moderate interobserver agreement when evaluating the RSNA chest CT classification system for COVID-19 against RT-PCR results. The study reported that 76.9%–96.6% of "typical" scans, 51.2%–64.1% of "indeterminate" scans, 2.8%–5.3% "atypical" scans, and 20%–25% of "negative pneumonia" scans returned RT-PCR positive results confirming COVID-19 for the corresponding patients [69,77].

As for "AI-assisted diagnostic" using CT, the diagnostic precision of the model is often calculated as the ability to distinguish between COVID-19 and other pneumonia cases, to quantitatively assess the disease severity and progression, and to segment the COVID-19 infected regions inside the lung. The deep-learning powered AI systems using CT images are reported to achieve COVID-19 identification accuracy at the level of >90% in the

disease classification task, AUC score of >96% in discriminating between severe and nonsevere stages, and an average Dice coefficient of 75%, while comparing the lung segmentation performance against expert annotations [74–76,78,79].

2.4.10 Benefits and limitations of CT-based diagnosis

CT test for COVID-19 can be considered as an opening into the disease pathology that could provide important insights into diagnosis and progression [77]. CT-scan may facilitate rapid diagnosis of COVID-19 as there is a specific infection pattern characterizing the typical CT features observed in frontier radiological reports. CT-scan can early detect COVID-19 in suspected patients bearing negative RT-PCR tests, even in asymptotic patients or before the onset of the symptoms [24].

On the contrary, performing CT routinely for a large population is not feasible and carries further risks, mainly due to limited personal protective equipment (PPE) resources, increased risk of viral transmission due to the proximity of patients and radiology technicians, and exposure to additional ionizing radiation [67]. Similar to plain radiography, CT utilizes X-ray radiation to produce images; however, the radiation doses from CT are higher due to multiple exposures [31].

2.4.11 Case study: radiology observations vs. CAD

A case study is extracted from [76], in which the radiological images of confirmed COVID-19 cases were compared against the "AI assisted diagnostic." The selected study evaluated the COVID-19 prediction performance of the proposed AI algorithm on a multinational dataset of CT images associated with COVID-19 patients.

The specificity or true positive rate of the AI-based findings were analyzed with visual assessment and examination of the Grad-CAM representation for some COVID-19 positive instances from the test image sets. Fig. 2.2 shows the Grad-CAM visualization of region-based activation map of the classes from the segmented and cropped lung images are shown for five representative patients with COVID-19. These five representative CT images exhibit the disease situations with different amounts of disease burden. Assessment of these Grad-CAM-based saliency maps demonstrates that the AI algorithm was able to find a consistent activation pattern in the peripheral regions of the lung, coherent with the radiological observation associated with COVID-19 related pneumonia.

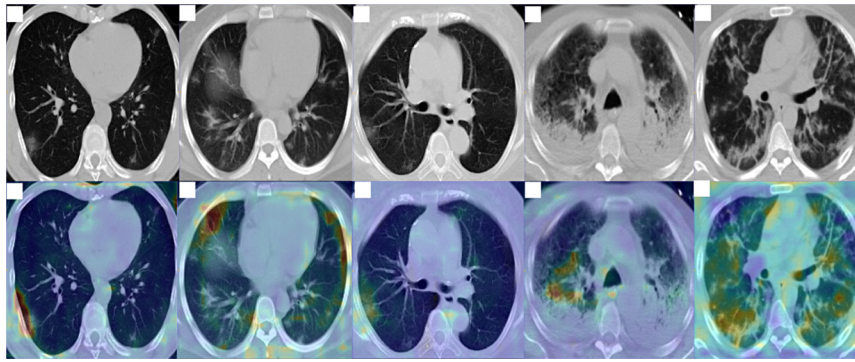

Figure 2.2 Grad-CAM visualization of the activation maps for five representative COVID-19 patients from the test set used in [76]. Within the heatmap, the red areas indicate the class activation with relation to COVID-19 prediction (For a color illustration of this figure, please see the e-book chapter). Note, all the images were correctly predicted positive by the AI algorithm. *Image courtesy [76].*

2.4.12 Lung ultrasound imaging modality

Ultrasound is an imaging modality utilizing high-frequency sound waves to provide cross-sectional images of the organs inside the body without using any radiation. The ultrasound imaging uses a small probe or a transducer, which emits sound waves or echoes at a certain frequency and collects the returning echoes at frequencies dependent on the internal tissues through which the sound waves travel. The sound waves bounced back to the probe are digitally transformed to echoes and dots on the monitoring screen. The digital images are acquired in real-time and can be obtained in any imaging plane. The ultrasound imaging is a non-invasive medical test that can be used for diagnosis and treatments [31].

2.4.13 COVID-19 diagnosis using lung ultrasound

Preliminary investigations on Chinese patients recommends that lung ultrasound imaging may have potentiality while evaluating the 20 patients with COVID-19 [29]. A few other studies also described the ultrasonographic signs and patterns related to COVID-19 [80–82]. The principal manifestations in lung ultrasound examinations are described below:

- Multiple B-lines in variety of patterns ranging from focal to diffuse, occasionally manifesting as a light beam sign
- Rough and thickened pleural line with discontinuity
- Subpleural and alveolar consolidations

- Restitution of aeration in the course of recovery through the reappearance of A-lines.

In ultrasonographic findings, focal B-lines can be considered as the main feature in the early course and in mild infection state; whereas alveolar interstitial consolidation is treated as the focal feature in the progression stage and in the critically ill patients. On the other hand, appearance of A-lines can be seen during the recovery stage [80].

2.4.13.1 Computer-aided diagnosis using lung ultrasound

A handful of "AI-assisted diagnostic" research was conducted using lung ultrasound imaging as input data. The pioneer of those is POCOVID-NET study by Born et al. [83]. In this research, the authors first put together a lung ultrasound dataset named as POCUS comprising 1103 images sampled from 64 videos; among those, 654 belong to COVID-19 positive patients, 277 to bacterial pneumonia cases and 172 to the healthy control group. A deep CNN model called POCOVID-NET was developed based on this three-class POCUS dataset. The model used the VGG-16 as the base convolutional architecture and was pretrained on ImageNet to extract the low-level image features such as edges, shapes, and textures. During the model training, the weights of last three layers were fine-tuned on the POCUS data, while using the pretrained values for other weights. Data augmentation techniques such as rotation, horizontal and vertical flips, etc. were also applied to increase the diversity of the dataset.

2.4.13.2 Diagnostic precision of ultrasound-based diagnosis

A clinical study evaluating the diagnostic precision of bedside ultrasound as a noninvasive assessment of lung lesions in patients with COVID-19 found that the ultrasound imaging scores exhibit relatively lower sensitivity for mild to moderate patients [84]. However, for patients with severe lung regions, the ultrasound score was found to be highly sensitive.

In the case of AI-assisted diagnostic using ultrasound imaging, the POCOVID-Net study [83] showed that the deep learning model achieved the highest 98% of sensitivity of identifying COVID-19 using ultrasound imaging frames. 628 cases among 654 COVID-19 positive patients were identified accurately by the POCOVID-Net model. For the other two classes (bacterial pneumonia and healthy control), the sensitivity rates were 93% and 55%, respectively.

2.4.13.3 Benefits and limitations of ultrasound-based diagnosis

The ultrasound imaging demonstrates promising performances for COVID-19 identification both in clinical and computational evaluations

[83,84]. Due to its higher sensitivity of recognizing COVID-19 related pneumonia, ultrasound imaging can be used as a rapid diagnostic tool. Ultrasound imaging has numerous benefits over other biomedical diagnostic imaging tools including its ease of execution and repeatability, noninvasiveness, noninvolvement of radiation, execution without relocating, and ease of disinfection at the bedside. Moreover, the ultrasound exams are very cost-effective compared to chest X-ray and CT-scans. The ultrasound devices are small, portable, and low priced, making this type of imaging exceedingly suitable to use in a resource-constrained environment [83].

Although ultrasound imaging can be used for rapid diagnosis for identifying lung lesions in the patients with COVID-19, a comprehensive evaluation of the diagnostic efficacy of the ultrasound imaging is yet to be performed. Therefore, in practice, lung ultrasound is not used as a first-line diagnostic procedure. Even if there is an ultrasound examination, the key diagnostic decisions should be taken either using a CT scans or a RT-PCR test.

2.4.14 Conclusion

The chest and/or lung imaging based diagnosis turns out to be one of the principal diagnostic tools for COVID-19 identification. As SARS-CoV-2 causes severe distresses on respiratory system leading to pneumonia-like symptoms, all three major imaging modalities involving chest and lung, namely CXR, CT-scans and lung ultrasounds provide invaluable information about the pulmonary abnormalities caused by this viral infection. Additionally, these imaging tools can be used extensively for grading the severity of the disease, and monitoring the disease progression. However, to manually extract the radiological findings in these images, highly qualified and experienced radiologists are needed. To reduce the burden on radiologists for interpreting these images, "AI-assisted diagnostic" could come into the forefront now. These images can be now be readily input to the AI system, and the diagnostic results can be received within a few seconds. The power of AI further enhances the utility of these imaging modalities concerning diagnosis, severity grading, and progressive monitoring of patients with COVID-19.

References

[1] World Health Organization (WHO), 2020. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [online]. Available from: https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19) (accessed 19.06.20).

[2] Worldometers, 2020. Coronavirus Update (Live) [online]. Available from: https://www.worldometers.info/coronavirus/ (accessed: 19.06.20).
[3] Tan, R., 2020. COVID-19 Diagnostics Explained, Asian Scientist, April 8 [online]. Available from: www.asianscientist.com/2020/04/features/covid-19-diagnostics-explained/ (accessed: 19.06.20).
[4] Elisagenie, 2020. Rapid COVID-19 Antibody Detection Tests: Principles and Methods [online]. Available from: https://www.elisagenie.com/rapid-covid19-antibody-detection-tests-principles-and-methods (accessed: 22.08.20).
[5] J. Xia, J. Tong, M. Liu, Y. Shen, D. Guo, Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection, J. Med. Virol. 92 (6) (2020) 589–594.
[6] American College of Physicians (ACP)COVID-19 found in sputum and feces samples after pharyngeal specimens no longer positive, Science Daily (2020) March 30 [online]. Available from: www.sciencedaily.com/releases/2020/03/ 200330110348.htm (accessed: 19.06.20).
[7] S.A. Kujawski, K.K. Wong, J.P. Collins, L. Epstein, M.E. Killerby, C.M. Midgley, G.R. Abedi, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States, Nature Med. 26 (2020) 861–868.
[8] H.D. VanGuilder, K.E. Vrana, W.M. Freeman, Twenty-five years of quantitative PCR for gene expression analysis, Biotechniques 44 (5) (2008) 619–626.
[9] Sigma-Aldrich 2020. RT-PCR -- Reverse Transcription PCR,online. Available from: https://www.sigmaaldrich.com/life-science/molecular-biology/pcr/rt-pcr.html/ (Accessed: Dec 06, 2020)
[10] B. Böger, M.M. Fachi, R.O. Vilhena, A. de Fátima Cobre, F.S. Tonin, R. Pontarolo, Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19, Am. J. Infect. Control (2020).
[11] Centers for Disease Control and Prevention (CDC), 2020. Serology Testing for COVID-19 at CDC [online]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/serology-testing.html#:~:text=CDC's%20serologic%20test%20is%20an,the%20National%20Institutes%20of%20Health) (accessed: 21.08.20).
[12] Creative-Diagnostics (CD), 2020. Chemiluminescence Immunoassay Guide [online]. Available from: https://www.creative-diagnostics.com/Chemiluminescence-Immunoassay-guide.htm (accessed: 19.06.20).
[13] American Society for Microbiology (ASM), 2020. COVID-19 Serology Testing Explained [online]. Available from: https://asm.org/Articles/2020/May/COVID-19-Serology-Testing-Explained (accessed: 22.08.20).
[14] L.J. Carter, L.V. Garner, J.W. Smoot, Y. Li, Q. Zhou, C.J. Saveson, J.M. Sasso, A.C. Gregg, D.J. Soares, T.R. Beskid, S.R. Jervey, Assay techniques and test development for COVID-19 diagnosis, ACS Central Science 6 (5) (2020) 591–605.
[15] X. Cai, J. Chen, J. Hu, Q. Long, H. Deng, K. Fan, P. Liao, B. Liu, G. Wu, Y. Chen, Z. Li, A Peptide-based magnetic chemiluminescence enzyme immunoassay for serological diagnosis of corona virus disease 2019 (COVID-19), medRxiv (2020)doi: 10.1101/2020.02.22.20026617.
[16] Diazyme Laboratories Inc (DLI)Announces Availability of COVID-19 Antibody Tests. News & Media Diazyme Laboratories Inc, March 23 [online]. Available from: www.diazyme.com/diazyme-laboratories-inc-announces-availability-of-covid-19-antibody-tests (accessed: 19.06.20).
[17] D.T.H.D. Moura, T.R. McCarty, I.B. Ribeiro, M.P. Funari, P.V.A.G.D. Oliveira, A.A.D. Miranda Neto, E.S.D. Monte Júnior, F. Tustumi, W.M. Bernardo, E.G.H.D. Moura, C.C. Thompson, Diagnostic characteristics of serological-based COVID-19 testing: a systematic review and meta-analysis, Clinics (2020) 75.

[18] M.L. Bastos, G. Tavaziva, S.K. Abidi, J.R. Campbell, L.P. Haraoui, J.C. Johnston, Z. Lan, S. Law, E. MacLean, A. Trajman, D. Menzies, Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis, BMJ (2020) 370.
[19] B. Freeman, S. Lester, L. Mills, M.A.U. Rasheed, S. Moye, O. Abiona, G.B. Hutchinson, M. Morales-Betoulle, I. Krapinunaya, A. Gibbons, C.F. Chiang, Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and serosurveillance, bioRxiv (2020).
[20] ACROBiosystems (ACROB), 2020. Overview of ELISA Testing for COVID-19 Antibodies. News-Medical [online]. Available from: from https://www.news-medical.net/whitepaper/20200616/Overview-of-ELISA-Testing-for-COVID-19-Antibodies.aspx. (accessed: 19.0620).
[21] S. Duchesne, D. Gourdeau, P. Archambault, C. Chartrand-Lefebvre, L. Dieumegarde, R. Forghani, .C. Gagne, A. Hains, D. Hornstein, H. Le, S. Lemieux, Tracking and predicting covid-19 radiological trajectory using deep learning on chest x-rays: initial accuracy testing, medRxiv (2020).
[22] Radiopaedia, 2020. COVID-19 Radiology Reference Article [online]. Available from: https://radiopaedia.org/articles/covid-19-4?lang=us (accessed: 20.06.20).
[23] Y. Li, L. Xia, Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management, Am. J. Roentgenol. 214 (6) (2020) 1280–1286.
[24] T. Ai, Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao, Z. Sun, L. Xia, Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases, Radiology (2020) 200642.
[25] Y. Fang, H. Zhang, J. Xie, M. Lin, L. Ying, P. Pang, W. Ji, Sensitivity of chest CT for COVID-19: comparison to RT-PCR, Radiology (2020) 200432.
[26] J. Won, S. Lee, M. Park, T.Y. Kim, M.G. Park, B.Y. Choi, D. Kim, H. Chang, V.N. Kim, C.J. Lee, Development of a laboratory-safe and low-cost detection protocol for SARS-CoV-2 of the Coronavirus Disease 2019 (COVID-19), Exp. Neurobiol. 29 (2) (2020) 107.
[27] J.P. Kanne, Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: key points for the radiologist, Radiology 295 (1) (2020) 16–17.
[28] A. Bernheim, X. Mei, M. Huang, Y. Yang, Z.A. Fayad, N. Zhang, K. Diao, B. Lin, X. Zhu, K. Li, S. Li, Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection, Radiology (2020) 200463.
[29] X. Xie, Z. Zhong, W. Zhao, C. Zheng, F. Wang, J. Liu, Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing, Radiology (2020) 200343–1200343.
[30] Q.Y. Peng, X.T. Wang, L.N. Zhang, Chinese Critical Care Ultrasound Study Group-Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic, Intensive Care Med. (2020) 1.
[31] World Health Organization (WHO), 2020. Diagnostic imaging [online]. Available from; https://www.who.int/diagnostic_imaging/imaging_modalities/dim_plain-radiography/en/ (accessed: 20.08.20).
[32] J.C.L. Rodrigues, S.S. Hare, A. Edey, A. Devaraj, J. Jacob, A. Johnstone, R. McStay, A. Nair, G. Robinson, An update on COVID-19 for the radiologist-A British society of Thoracic Imaging statement, Clin. Radiol. 75 (5) (2020) 323–325.
[33] H.Y.F. Wong, H.Y.S. Lam, A.H.T. Fong, S.T. Leung, T.W.Y. Chin, C.S.Y. Lo, M.M.S. Lui, J.C.Y. Lee, K.W.H. Chiu, T. Chung, E.Y.P. Lee, Frequency and distribution of chest radiographic findings in COVID-19 positive patients, Radiology (2020) 201160.
[34] The British Society of Thoracic Imaging (BSTI), 2020. COVID-19 BSTI Reporting templates [online]. Available from: https://www.bsti.org.uk/covid-19-resources/covid-19-bsti-reporting-templates/ (accessed: 25.07.20).
[35] J.P. Cohen, P. Morrison, L. Dao, COVID-19 image data collection, arXiv preprint arXiv:2003 (2020) 11597.

[36] Italian Society of Medical and Interventional Radiology (SIRM), 2020. COVID-19 dataset SIRM [online]. Available from: https://www.sirm.org/category/senza-categoria/covid-19 (accessed: 25.05.20).
[37] M.E. Chowdhury, T. Rahman, A. Khandakar, R. Mazhar, M.A. Kadir, Z.B. Mahbub, K.R. Islam, M.S. Khan, A. Iqbal, N. Al-Emadi, M.B.I. Reaz, Can AI help in screening viral and COVID-19 pneumonia?, arXiv preprint arXiv:2003 (2020) 13145.
[38] M.D.L.I. Vayá, J.M. Saborit, J.A. Montell, A. Pertusa, A. Bustos, M. Cazorla, J. Galant, X. Barber, D. Orozco-Beltrán, F. Garcia, M. Caparrós, BIMCV COVID-19+: a large annotated dataset of RX and CT images from COVID-19 patients, arXiv preprint arXiv:2006 (2020) 01174.
[39] R.M. Pereira, D. Bertolini, L.O. Teixeira, C.N. Silla Jr., Y.M. Costa, COVID-19 identification in chest X-ray images on flat and hierarchical classification scenarios, Comput. Methods Progr. Biomed. (2020) 105532.
[40] M.A. Elaziz, K.M. Hosny, A. Salah, M.M. Darwish, S. Lu, A.T. Sahlol, New machine learning method for image-based diagnosis of COVID-19, PLOS ONE 15 (6) (2020) e0235187.
[41] S. Rajpal, N. Kumar, A. Rajpal, COV-ELM classifier: An Extreme Learning Machine based identification of COVID-19 using Chest-ray Images, arXiv preprint arXiv:2007 (2020) 08637.
[42] J. Irvin, P. Rajpurkar, M. Ko, Y. Yu, S. Ciurea-Ilcus, C. Chute, H. Marklund, B. Haghgoo, R. Ball, K. Shpanskaya, J. Seekins, 2019. July. Chexpert: A large chest radiograph dataset with uncertainty labels and expert comparison. In Proceedings of the AAAI Conference on Artificial Intelligence Vol. 33, pp. 590–597.
[43] H.H. Pham, T.T. Le, D.T. Ngo, D.Q. Tran, H.Q. Nguyen, Interpreting chest X-rays via CNNs that exploit hierarchical disease dependencies and uncertainty labels, arXiv preprint arXiv:2005 (2020) 12734.
[44] T. Gabruseva, D. Poplavskiy, A. Kalinin, 2020. Deep Learning for Automatic Pneumonia Detection. In Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops, pp. 350–351.
[45] N. Bansal, S. Sridhar, 2020. Classification of X-ray images for detecting Covid-19 using deep transfer learning.
[46] P.R. Bassi, R. Attux, A deep convolutional neural network for COVID-19 detection using chest X-rays, arXiv preprint arXiv:2005 (2020) 01578.
[47] J. Zech, Reproduce-chexnet, 2018. URL https://github com/jrzech/283 reproduce-chexnet, 284.
[48] H. Benbrahim, H. Hachimi, A. Amine, Deep transfer learning with Apache Spark to detect COVID-19 in chest X-ray images, Roman. J. Inform. Sci. Technol. 23 (2020) S117–S129.
[49] M. Zaharia, R.S. Xin, P. Wendell, T. Das, M. Armbrust, A. Dave, X. Meng, J. Rosen, S. Venkataraman, M.J. Franklin, A. Ghodsi, Apache spark: a unified engine for big data processing, Commun. ACM 59 (11) (2016) 56–65.
[50] J. de Moura, J. Novo, M. Ortega, Fully automatic deep convolutional approaches for the analysis of Covid-19 using chest X-ray images, medRxiv (2020).
[51] S. Chatterjee, F. Saad, C. Sarasaen, S. Ghosh, R. Khatun, P. Radeva, G. Rose, S. Stober, O. Speck, A. Nürnberger, Exploration of Interpretability Techniques for Deep COVID-19 Classification using Chest X-ray Images, arXiv preprint arXiv:2006. (2020) 02570.
[52] B. Ghoshal, A. Tucker, Estimating uncertainty and interpretability in deep learning for coronavirus (COVID-19) detection, arXiv preprint arXiv:2003 (2020) 10769.
[53] H. Khan, A. Sohail, M. Zafar, A. Khan, 2020. Coronavirus Disease Analysis using Chest X-ray Images and a Novel Deep Convolutional Neural Network. Pre-Print.
[54] D. Lv, W. Qi, Y. Li, L. Sun, Y. Wang, A cascade network for detecting COVID-19 using chest x-rays, arXiv preprint arXiv:2005 (2020) 01468.

[55] A. Narin, C. Kaya, Z. Pamuk, Automatic detection of coronavirus disease (covid-19) using x-ray images and deep convolutional neural networks, arXiv preprint arXiv:2003 (2020) 10849.
[56] Y. Oh, S. Park, J.C. Ye, Deep learning covid-19 features on cxr using limited training data sets, IEEE Trans. Med. Imaging 39 (8) (2020) 2688–2700.
[57] S. Rajaraman, J. Siegelman, P.O. Alderson, L.S. Folio, L.R. Folio, S.K. Antani, Iteratively pruned deep learning ensembles for COVID-19 detection in chest X-rays, arXiv preprint arXiv:2004 (2020) 08379.
[58] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, D.S. Hui, B. Du, Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (18) (2020) 1708–1720.
[59] G.D. Rubin, C.J. Ryerson, L.B. Haramati, N. Sverzellati, J.P. Kanne, S. Raoof, N.W. Schluger, A. Volpi, J.J. Yim, I.B. Martin, D.J. Anderson, The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society, Chest (2020).
[60] A. Jacobi, M. Chung, A. Bernheim, C. Eber, Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review, Clin. Imaging (2020).
[61] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[62] F. Pan, T. Ye, P. Sun, S. Gui, B. Liang, L. Li, D. Zheng, J. Wang, R.L. Hesketh, L. Yang, C. Zheng, Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia, Radiology (2020).
[63] F. Shi, L. Xia, F. Shan, D. Wu, Y. Wei, H. Yuan, H. Jiang, Y. Gao, H. Sui, D. Shen, Large-scale screening of Covid-19 from community acquired pneumonia using infection size-aware classification, arXiv preprint arXiv:2003 (2020) 09860.
[64] E.Y. Lee, M.Y. Ng, P.L. Khong, COVID-19 pneumonia: what has CT taught us?, Lancet Infect. Dis. 20 (4) (2020) 384–385.
[65] J. Zhao, Y. Zhang, X. He, P. Xie, COVID-CT-Dataset: a CT scan dataset about COVID-19, arXiv preprint arXiv:2003 (2020) 13865.
[66] S. Perlman, 2020. Another decade, another coronavirus.
[67] J.P. Kanne, B.P. Little, J.H. Chung, B.M. Elicker, L.H. Ketai, Essentials for radiologists on COVID-19: an update—radiology scientific expert panel, Radiology (2020).
[68] Y. Pan, H. Guan, S. Zhou, Y. Wang, Q. Li, T. Zhu, Q. Hu, L. Xia, Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China, Eur. Radiol. (2020) 1–4.
[69] S. Simpson, F.U. Kay, S. Abbara, S. Bhalla, J.H. Chung, M. Chung, T.S. Henry, J.P. Kanne, S. Kligerman, J.P. Ko, H. Litt, Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA, Radiology: Cardiothor. Imaging 2 (2) (2020) e200152.
[70] W. Zhao, Z. Zhong, X. Xie, Q. Yu, J. Liu, Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study, Am. J. Roentgenol. 214 (5) (2020) 1072–1077.
[71] L. Li, L. Qin, Z. Xu, Y. Yin, X. Wang, B. Kong, J. Bai, Y. Lu, Z. Fang, Q. Song, K. Cao, Artificial intelligence distinguishes COVID-19 from community acquired pneumonia on chest CT, Radiology (2020) 200905.
[72] S. Jin, B. Wang, H. Xu, C. Luo, L. Wei, W. Zhao, X. Hou, W. Ma, Z. Xu, Z. Zheng, W. Sun, AI-assisted CT imaging analysis for COVID-19 screening: building and deploying a medical AI system in four weeks, medRxiv (2020).
[73] H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, Y. Fan, C. Zheng, Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect. Dis. (2020).

[74] X. Mei, H.C. Lee, K.Y. Diao, M. Huang, B. Lin, C. Liu, Z. Xie, Y. Ma, P.M. Robson, M. Chung, A. Bernheim, Artificial intelligence–enabled rapid diagnosis of patients with COVID-19, Nat. Med. (2020) 1–5.
[75] R. Hu, G. Ruan, S. Xiang, M. Huang, Q. Liang, J. Li, Automated diagnosis of COVID-19 using deep learning and data augmentation on chest, medRxiv (2020).
[76] S.A. Harmon, T.H. Sanford, S. Xu, E.B. Turkbey, H. Roth, Z. Xu, D. Yang, A. Myronenko, V. Anderson, A. Amalou, M. Blain, Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, Nat. Commun. 11 (1) (2020) 1–7.
[77] T.M. de Jaegere, J. Krdzalic, B.A. Fasen, R.M. Kwee, COVID-19 C.T. Investigators South-East Netherlands (CISEN) study groupRadiological Society of North America Chest CT Classification System for Reporting COVID-19 Pneumonia: Interobserver Variability and Correlation with RT-PCR, Radiology: Cardiothor. Imaging 2 (3) (2020) e200213.
[78] Z. Li, Z. Zhong, Y. Li, T. Zhang, L. Gao, D. Jin, Y. Sun, X. Ye, L. Yu, Z. Hu, J. Xiao, From community acquired pneumonia to COVID-19: a deep learning based method for quantitative analysis of COVID-19 on thick-section CT Scans, medRxiv (2020).
[79] S. Wang, Y. Zha, W. Li, Q. Wu, X. Li, M. Niu, M. Wang, X. Qiu, H. Li, H. Yu, W. Gong, A fully automatic deep learning system for COVID-19 diagnostic and prognostic analysis, Eur. Respir. J. (2020).
[80] Y. Huang, S. Wang, Y. Liu, Y. Zhang, C. Zheng, Y. Zheng, C. Zhang, W. Min, H. Zhou, M. Yu, M. Hu, 2020. A preliminary study on the ultrasonic manifestations of peripulmonary lesions of non-critical novel coronavirus pneumonia (COVID-19). Available at SSRN 3544750.
[81] E. Poggiali, A. Dacrema, D. Bastoni, V. Tinelli, E. Demichele, P. Mateo Ramos, T. Marcianò, M. Silva, A. Vercelli, A. Magnacavallo, Can lung US help critical care clinicians in the early diagnosis of novel coronavirus (COVID-19) pneumonia?, Radiology 295 (3) (2020) E6–E16.
[82] G. Volpicelli, L. Gargani, Sonographic signs and patterns of COVID-19 pneumonia, Ultrasound J. 12 (1) (2020) 1–3.
[83] J. Born, G. Brändle, M. Cossio, M. Disdier, J. Goulet, J. Roulin, N. Wiedemann, POCOVID-Net: automatic detection of COVID-19 from a new lung ultrasound imaging dataset (POCUS), arXiv preprint arXiv:2004 (2020) 12084.
[84] W. Lu, S. Zhang, B. Chen, J. Chen, J. Xian, Y. Lin, H. Shan, Z.Z. Su, A clinical study of noninvasive assessment of lung lesions in patients with coronavirus disease-19 (COVID-19) by bedside ultrasound, Ultraschall in der Medizin-European Journal of Ultrasound 41 (03) (2020) 300–307.