Summer Training Report

on

Role of X-ray & CT scan during Covid-19

by

Aditya Singh

Under the guidance of

Dr. P.R Sodani

MBA Hospital and Health Management

2019-21

ACKNOWLEDGEMENT

Learning is a never ending process. Our quest to learn more and more by grabbing every possible opportunity that comes our way, proves to be the reason behind our success one day.

I would like to thank the management for providing me with this learning opportunity, which has enhanced my knowledge related to radiography, role of X-rays and CT during the Covid-19 pandemic and how has radiography contributed towards diagnosing the Covid-19 patients in such odd situations. Working on this report has made it possible for me to explore the topic in all possible dimensions to extract best out of all the data available and turn this opportunity into a beautiful learning experience.

My sincere thanks to my mentor **Dr.P.R Sodani** who has been a constant support and has guided me in the correct direction throughout my learning process.

My heartfelt gratitude and appreciation are also extended towards **Dr. Sujata Verma** (Faculty-IIHMR) and **Ms. Disha Faujdar** for their useful advice and constant support in the completion of my project report.

Lastly, I admit my inability to express my emotions through words for my loving parents and for their encouragement, support and constant faith in me.

Above all I thank the Almighty for giving me patience and strength to overcome the difficulties, which crossed my way in accomplishment at this endeavour.

TABLE OF CONTENTS

ACRONYMS/ABBREVIATIONS

1. CT/CAT- Computed Tomography / Computed Axial Tomography
2. 3D- Three Dimensional
3. Covid-19- Coronavirus Disease
4. SARS-CoV2- Severe Acute Respiratory Syndrome Coronavirus 2
5. 2019-nCoV- 2019 Novel Coronavirus
6. WHO- World Health Organization
7. H1N1- Swine Flu Virus
8. R&D- Research and Development
9. IBV- Infectious Bronchitis Virus
10. B814- One of the first coronavirus of human origin
11. 229E- One of the first coronavirus of human origin
12. OC43- Family of coronavirus
13. SARS-CoV- Severe Acute Respiratory Syndrome Coronavirus
14. HCoV- Human Coronavirus
15. NL63- Family of Coronavirus
16. HKU1- Family of Coronavirus
17. MERS-CoV- Middle East Respiratory Syndrome Coronavirus
18. SARS- Severe Acute Respiratory Syndrome
19. RNA- Ribonucleic Acid
20. MERS- Middle East Respiratory Syndrome
21. PPE- Personal Protective Equipment
22. ARDS- Acute Respiratory Distress Syndrome
23. GGO- Ground Glass Opacity
24. CNN- Convolutional Neural Network
25. SVM- Support Vector Machine
26. OPD- Outpatient Department
27. MD- Medical Devices
28. FDA- Food and Drug Administration
29. NDC- National Drug Code

SUMMER TRAINING REPORT-PART 1

ROLE OF X-RAY AND COMPUTED TOMOGRAPHY IN COVID-19

INTRODUCTION

WHAT ARE X-RAYS?

"**X-ray** or radiography uses a very small dose of ionizing radiation to produce pictures of the body's internal structures. X-rays are the oldest and most frequently used form of medical imaging. They are often used to help diagnosed fractured bones, look for injury or infection and to locate foreign objects in soft tissue. Some x-ray exams may use an iodine-based contrast material or barium to help improve the visibility of specific organs, blood vessels, tissues or bone." (radiologyinfor.org)

WHAT IS CT SCAN?

"Computed tomography, more commonly known as a CT or CAT scan, is a diagnostic medical imaging test. Like traditional x-rays, it produces multiple images or pictures of the inside of the body. The cross-sectional images generated during a CT scan can be reformatted in multiple planes. They can even generate three-dimensional images. These images can be viewed on a computer monitor, printed on film or by a 3D printer, or transferred to a CD or DVD. CT images of internal organs, bones, soft tissue and blood vessels provide greater detail than traditional x-rays, particularly of soft tissues and blood vessels. Using specialized equipment and expertise to create and interpret CT scans of the body, radiologists can more easily diagnose problems such as cancer, cardiovascular disease, infectious disease, appendicitis, trauma and musculoskeletal disorders." [2]

WHAT IS COVID-19?

"Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China. It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009." [3] "Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol based rub frequently and not touching your face. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice

respiratory etiquette (for example, by coughing into a flexed elbow).At this time, there are no specific vaccines or treatments for COVID-19. However, there are many ongoing clinical trials evaluating potential treatments. WHO will continue to provide updated information as soon as clinical findings become available." [4]

HISTORY OF X-RAY AND COMPUTED TOMOGRAPHY

On 8th November 1895, Wilhelm Conrad Roentgen discovered X-ray. W.C Roentgen worked as a professor at the University of Wuerzburg, Germany. In his laboratory, he was experimenting with a cathode ray tube. The tube started emitting a fluorescent glow of crystals. The cathode ray tube comprised of a glass envelope (bulb) with positive electrode and negative electrodes. Fluorescent glow was produced when high voltage was passed and air was released from the cathode ray tube. Then Roentgen covered the tube with black paper and discovered a green coloured fluorescent light being emitted by a material located a few feet away from the tube. He came to a conclusion that cathode ray tube was releasing a kind of ray which was novel. This unidentified ray could penetrate through heavy paper and could penetrate most of the substances by casting shadow of solid objects. W.C Roentgen later discovered that these rays could penetrate human tissues but not metallic objects and bones. The first experiment by W.C Roentgen was carried out on his wife Bertha, he captured the image of her hand with the help of X-Ray. W.C Roentgen did now knew what the mysterious ray were made up of, hence he named them X-Rays.

Invention of CT (Computed Tomography) scan took place in the year 1972 by Godfrey Hounsfield and Allan Cormack and were later awarded for their contribution towards medical and science with Nobel Peace prize. Between 1974 and 1976 CT scans had started installing and widely available after 1980. Multi slice CT being the latest technology advancement can collect more than 4 slices of data within 350ms as compared with the first version of CT scan machine developed by Godfrey Hounsfield which took many hours to collect the raw data. With the help of multi-slice CT, it only takes five seconds to ten seconds to scan the chest region. In the last 25 years, Computed Tomography has made vast advancement in terms of patient comfort, resolution & speed. The fast scan time of CT allows us to scan more anatomy in less time. Breathing and peristalsis during the scan leads to formation of artifacts but fast scanning is beneficial in removing artifacts. Now excellent image quality is possible along with low X-ray dose due to extensive R&D.

HISTORY OF CORONAVIRUS

During the 1930's the coronaviruses were discovered when IBV was responsible for causing acute respiratory infection in domesticated chickens. In 1931 M.C Hawn and Arthur Schalk discovered a novel respiratory infection of chickens in North Dakota. Listlessness and gasping was found in new born chicks due to the infection. 40-90 % was the mortality rate of the chicks. After six years Fred Beaudette and Charles Hudson isolated and cultivated the IBV which was responsible for the disease. Two more coronaviruses- mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGV) emerged and were successfully isolated. During that time it was not realized that these three different virus were related.

In the 1960's first corona virus in humans were discovered- B814 and 229E. Scottish virologist June Almeida in 1967 imaged the two new strains with electron microscopy. With the help of electron microscopy Almeida

was able to draw a conclusion that B814 and 229E were related to each other due to their club-like spikes and infectious bronchitis virus (IBV). In 1967 a group of researchers from National Institute of Health were able to isolate a new member of this new group of viruses with the help of organ culture and named this new strain as OC43. Even OC43 had club-like spikes just like the B814 and 229E virus. The infectious bronchitis virus (IBV) was later shown to be related to the mouse hepatitis virus (MHV). The infectious bronchitis virus (IBV) group was later called as **coronavirus**. Till some decades extensive studies were conducted on 229E and OC43 human coronavirus. Many human coronavirus have been identified since 2003- SARS-CoV in 2003, HCov NL63 in 2004, HCoV HKU1 in 2005, MERS-CoV in 2012 and SARS-CoV-2 in 2019.

COMPARISION OF COVID-19 WITH PREVIOUS SEVERE CORONAVIRUSES

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

MICROBIOLOGY

SARS-CoV is the virus responsible for causing SARS. When SARS-CoV (virus) was compared with previous animal and human coronaviruses it was phylogenetically distinct from them. SARS-CoV is a positive strand RNA virus that is part of the family of coronaviridae. It was identified in 2003.

EPIDEMIOLOGY

SARS has an incubation period of 2 to 7 days, for some cases it can be as long as 10 to 14 days and the mean time from symptom onset to hospitalization is 2-8 days. Close person to person contact was the primary reason through which SARS spread. SARS-CoV has a reproductive number of 0.3-4.1 and can be easily transmitted through respiratory droplets when exhaled by an infected person while coughing or sneezing. Some patients were called super-spreaders, they transmitted SARS to more than 100 contacts.

OUTBREAKS

SARS was recognized in March 2003 as a threat to the world, and appeared in Southern China in November 2002. It was spread across 5 continents and 33 countries. 8437 people were infected with SARS and 813 died. In India 3 cases were confirmed by laboratory with no death. China had the maximum number of cases i.e 5327 and highest number of deaths i.e 349. After 2004 no new cases of SARS were reported.

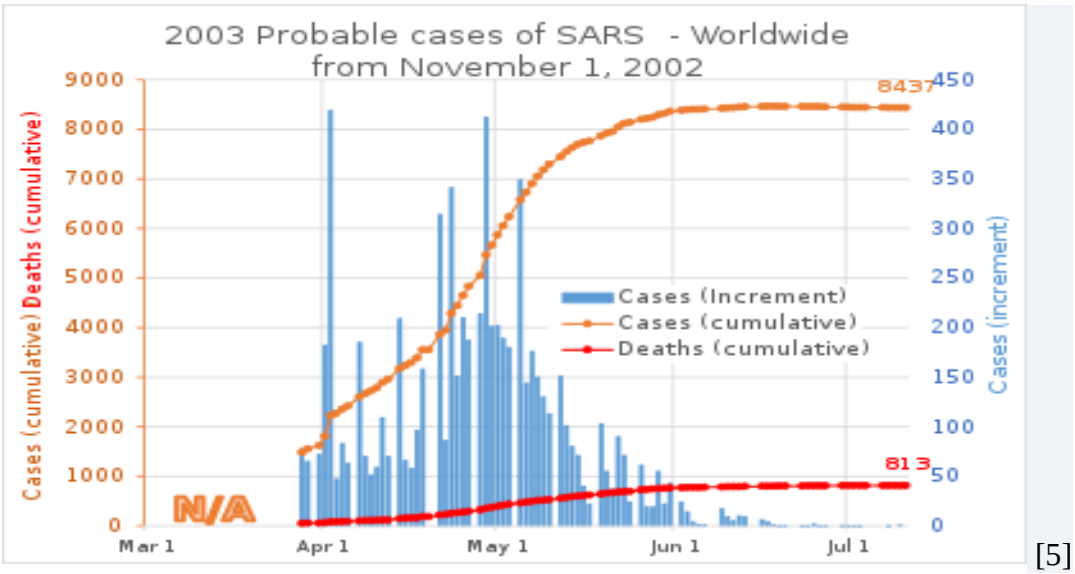
CLINICAL MANIFESTATIONS

The signs and symptoms of SARS were- High fever (temperature more than 38.8°C), headache, muscle pain and difficulty in breathing. After 2-7 days, patients developed a dry cough. One or two out of every 10 patients was suffering from diarrhea. Laboratory confirmed abnormalities such as lymphopenia, low platelet count, increased coagulation and mildly elevated serum hepatic enzymes. If the patient is older than 60 years, suffering from any comorbidity (diabetes, chronic lung disease etc) and is immunosuppressed then they have a higher risk of death. The reported rate of mortality is 9.6%.

INFECTION CONTROL ISSUES

SARS showed weakness in infection control practices globally. Around 21% of the infected people were healthcare professionals were infected around the world. Hong Kong and Hanoi (46% and 63% respectively)

experienced high rate of infection among healthcare professionals. Healthcare professionals who did not wear a mask had 12.6 time higher chance of getting infected as compared to those who wore masks during patient care activities. Other risk factors included- contact with respiratory tract secretions, exposure to body fluids of healthcare professional's eyes or mucous membranes, not using goggle, gowns or caps on a consistent basis and while performing activities such as bronchoscopy, mechanical ventilation, non-invasive ventilation, suctioning (open or tracheostomy) chest physiotherapy and nebulized medication administration. If patients are not placed in proper isolation rooms it would lead to transmission of disease within the hospital. Hand washing was also proved to be a preventive measure in multiple studies.



[5]

MIDDLE EAST RESPIRATORY SYNDROME (MERS)

MICROBIOLOGY

In 2012 MERS was recognized as a new respiratory disease. MERS-CoV (lineage 2C β CoV) was the virus responsible for causing MERS.MERS-CoV is a positive strand RNA virus which belongs to the **coronaviridae** family.

EPIDEMIOLOGY

By 25th September 2015 more than 24 countries reported cases of MERS. The incubation period for MERS is approximately 5 days (2-14 days). The median time from beginning of illness to hospitalization is 4 days and for death is 12 days. MERS-CoV was transmitted from animals to humans hence it is a zoonotic disease. MERS-CoV originated from bats and then transmitted to camels but the origin of the virus has still not been understood. Single humped camels are considered as a major reservoir host for MERS-CoV and an animal source of virus for human beings. MERS can be easily transmitted from person to person under close contact or while providing care to infected patient without protection with a reproductive number of 0.3-1.3. Studies have shown that healthcare professionals who came in contact with the patients reported low rate of transmission (1%-3%). However, limited infection control procedures led to increase in transmission in healthcare settings. The fatality rate for MERS is 34.3%.

OUTBREAKS

MERS was declared as an epidemic in the middle-east and WHO reported 1583 cases with 566 death. In 2012 the first case of MERS was reported in Saudi Arabia. With the help of retrospective studies it was confirmed that the first case occurred in Jordan in the summer of 2012. All the cases of MERS travelled to or lived in countries near the Arabian Peninsula. The largest outbreak of MERS apart from Saudi Arabia took place in Korea and China. WHO confirmed 186 total cases (Korea=185, China=1) and accounting 36 deaths. The last case of MERS was reported to the WHO on January 2020.

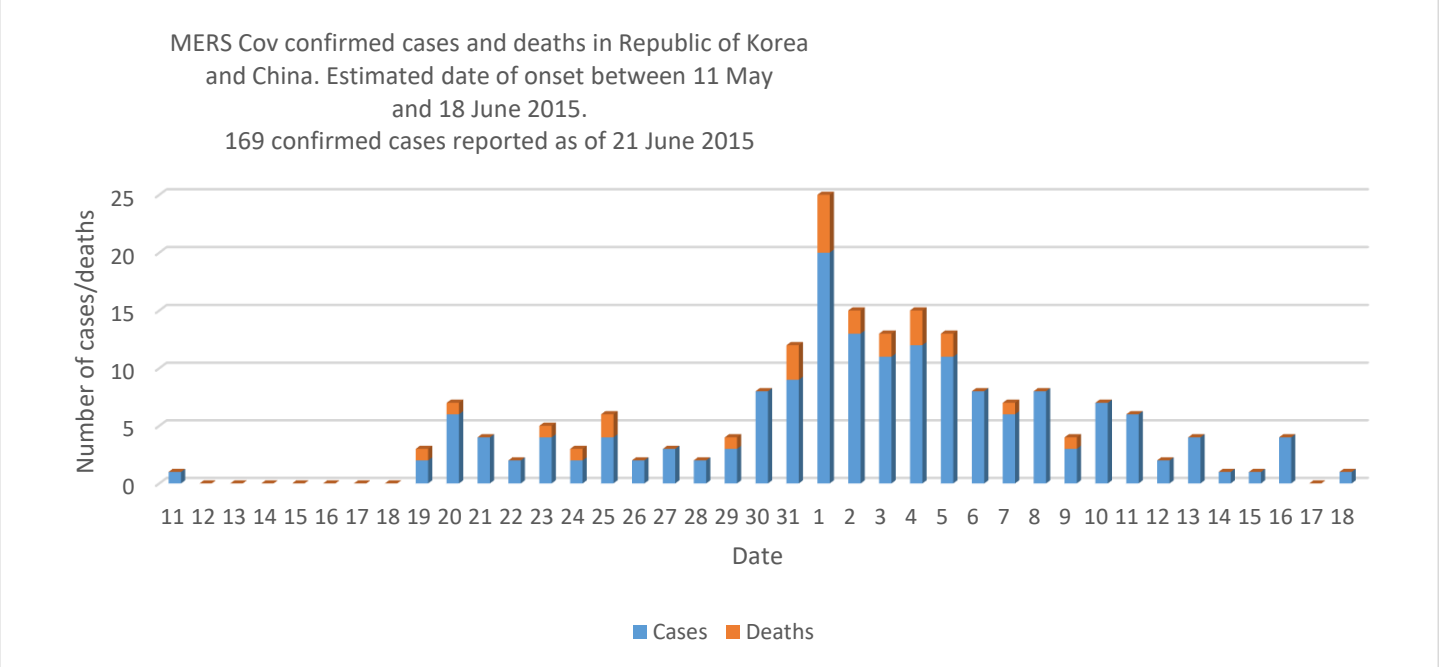
CLINICAL MANIFESTATIONS

The signs and symptoms of MERS were- Shortness of breath, cough and fever. Some patients developed pneumonia in their lungs. Condition of the patients ranged from asymptomatic or mild respiratory symptoms to severe acute respiratory disease and death. Patients frequently suffered from vomiting and diarrhea. If the patient is older than 60 years, suffering from any comorbidity (diabetes, chronic lung disease etc) and is immunosuppressed then they have a higher risk of death.

INFECTION CONTROL ISSUES

Many MERS outbreaks took place in healthcare facilities. An outbreak occurred affecting 23 patients while receiving hemodialysis - fatality rate was 65%.

High transmission rates were reported in healthcare facilities in an outbreak in South Korea. A hospital reported 11 tertiary cases, 25 secondary cases and only single primary case. Healthcare professionals were prone to acquire MERS. From June 2012 to September 2014 952 cases were reported in Saudi Arabia and 27% of them were healthcare professionals. Following are the factors which led to transmission of virus within the hospital- (a) Not islolating the patient because initial symptoms of MERS were not specific enough (b) Not following infection control practices (c) Overcrowding and close contact of patient to cases due to less healthcare facilities (d) High transmission due to aerosol generating procedures. Steps for preventing transmission- (a) Early identification of potential cases (b) Informing patients to call before coming at a healthcare facility if they had recent travel history from Middle East along with signs and symptoms of MERS (c) Following respiratory hygiene in emergency department and clinics.



CORONAVIRUS DIESEASE 2019(COVID-19)

MICROBIOLOGY

Covid-19 is caused by the virus SARS-CoV-2. The first case of Covid-19 was traced on 17th November 2019. SARS-CoV-2 virus & SARS-CoV virus are closely related to each other. As compared to its previous family of viruses, it has faster human to human transmission. . SARS-CoV-2 is a positive strand RNA virus which belongs to the **coronaviridae** family.

EPIDEMIOLOGY

Incubation period of Covid-19 is 2-14 days and an analysis of 181 patients confirmed that 97.5% of the cases developed symptoms within 11.5 days of infection. SARS-CoV-2 spreads from person to person under close contact. When someone who is suffering from Covid-19 they cough or breathe out tiny droplets that contain the virus which can enter via nose or mouth to a person who has not been infected. The reproductive number of Covid-19 is 5.7. Accounting more than 567,776 deaths the fatality rate of Covid-19 is 4.4%. Covid-19 is a zoonotic disease as it originated from bats and then transmitted to humans.

OUTBREAKS

The first outbreak was identified in Wuhan, China in the month of December 2019. Covid-19 was declared as a pandemic by the WHO on 11th March 2020. It is spread across 215 countries with 12,848,622cases and 567,776 deaths. The highest number of cases and deaths have been recorded in the United States of America (2,208,486 and 119,133 respectively).

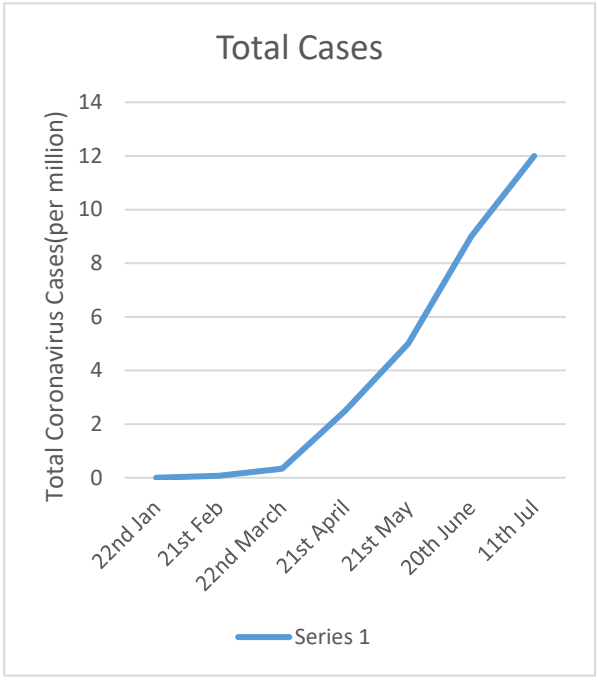
CLINICAL MANIFESTATIONS

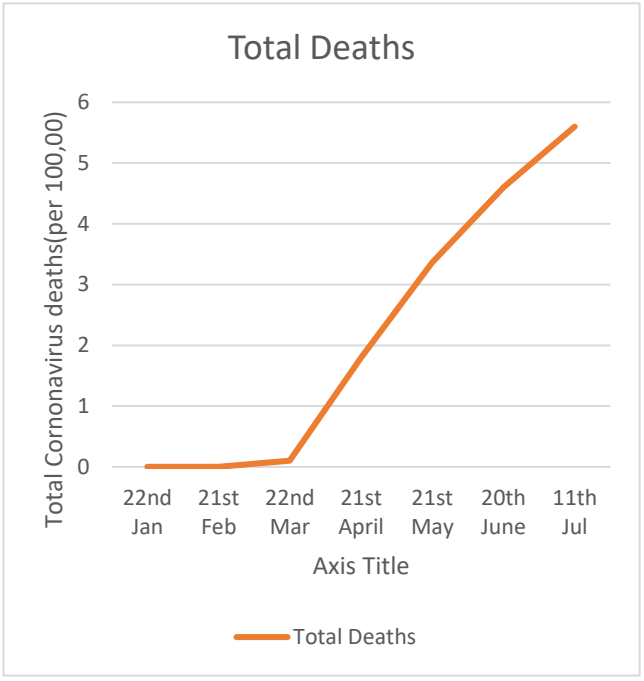
The signs and symptoms of Covid-19 were-cough. Loss of appetite, shortness of breath, joint pain, headache, chest pain and muscle pain. Severe patients develop pneumonia. Fever being the most common symptom of Covid-19 is variable in terms of severity of the disease. In some cases immunosuppressed, old and critically ill patients did suffer from fever at all. People who are 65 years and older, suffering from serious heart conditions, immunosuppressed, diabetes, undergoing dialysis and liver disease had higher risk for serious illness from Covid-19. Reported rate of mortality is 4.4%.

INFECTION CONTROL ISSUES

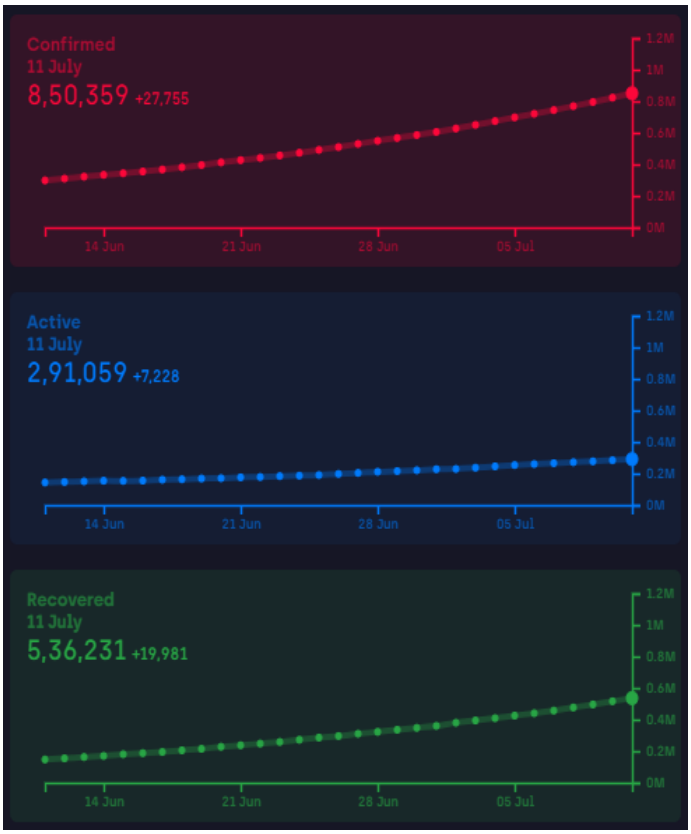
Early detection and isolation of patients, use of appropriate PPE while caring the Covid-19 patients, covering nose and mouth to contain the respiratory secretions. A report from China on Covid-19 stated that 43% of the patients out of 138 acquired infection from a healthcare facility. Washington state reported 81 residents, 34 staff members and 14 visitors got infected because of low standards of infection control was being followed. . Other risk factors included- contact with respiratory tract secretions, exposure to body fluids of healthcare professional's eyes or mucous membranes, not using PPE and while performing activities such as bronchoscopy, colonoscopy, filter changes on ventilator, manual ventilation before intubation, tracheotomy. When a suspected or confirmed Covid-19 is giving his/her oropharyngeal or nasopharyngeal specimen the healthcare worker should wear an N95 or higher level respirator, eye protection, gloves and a gown.

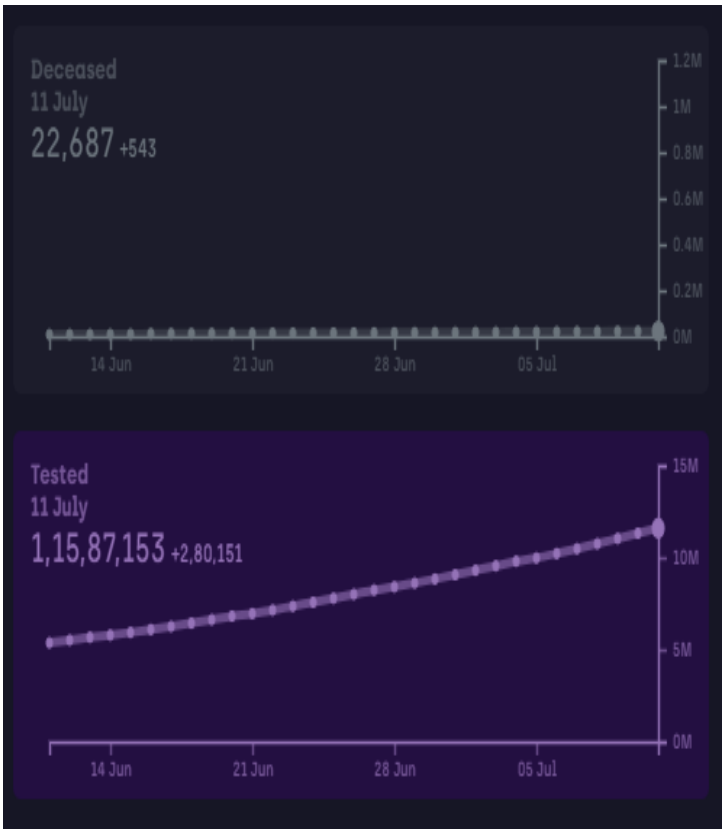
WORLDWIDE COVID-19 TOTAL CASES AND TOTAL DEATHS





COVID-19 TOTAL CASES AND TOTAL DEATHS IN INDIA





[6]

CHARACTERISTICS AND OTHER FACTORS	SARS	MERS	COVID-19
Total Cases	8096	2519	12,848,622

Total Deaths	774	866	567,766
Person to person transmission	Yes (droplet, contact)	Yes (droplet, contact)	Yes (droplet, contact)
Infection control risk	High	High	High
Years active & year identified	2002-2004 (2002 identified)	2012-present (2012 identified)	2019-present(2019)
Family	Coronaviridae	Coronaviridae	Coronaviridae
Genome	RNA	RNA	RNA
Endemic/Pandemic Location	China	Middle East	China
Reservoir	Bats, palm civet	Bats, camel	Bats
Incubation period	2-7 days	2-14 days	2-14 days
Reproduction number	0.3-4.1	0.3-1.3	5.7
Mortality rate	9.6%	34.4%	4.4%
Clinical therapy	Supportive	Supportive	Supportive

RATIONALE

The coronavirus disease (COVID-19) presents itself as a highly communicable pathogenic viral infection caused by SARS-CoV-2. The primary region of infection in Covid-19 are the lungs. Pneumonia and ARDS were the reason for death in severe cases. Eighty percent (80%) of the cases experienced mild symptoms, fourteen percent (14%) developed pneumonia, five percent (5%) suffered from organ failure or septic shock and two percent (2%) cases were fatal. Diagnostic plays a vital role in identifying the cases who have been infected. X-rays and CT scan provides the images of the human lungs with high sensitivity at ease and consumes less time. The image characteristics of the Covid-19 positive patients help us to study the condition of the patient along with time and when deep learning models are combined with X-rays and CT scan we get accurate results.

RESEARCH QUESTION

To study the role of x-rays and computed tomography in Covid-19?

RESEARCH OBJECTIVES

- To understand the image characteristics of novel coronavirus in x-rays.
- To understand the image characteristics of novel coronavirus in computed tomography
- Does deep learning help in deriving more accurate results or not.

LITERATURE REVIEW

Journal and Date	Title	Authors and Link	Main Question	Key Facts
"Pak J Med Sci. 2020 May"	"Chest X-rays findings in COVID 19 patients at a University Teaching Hospital - A descriptive study"	Durrani.M et al , Pakistan https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7306947/	"To analyze Chest X-ray findings in COVID 19 positive patients, presented at corona filtration center, Benazir Bhutto Hospital Rawalpindi"	***30 Covid-19** positive patients, mean age of patients- 44 (7-81 years) age range. Majority of the patients had complaints of cough(67%), fever(60%) and shortness of breath(37%). *93% patients showed abnormal chest radiograph * Most of the patients belonged to intermediate group due to bilateral, peripheral ground glass opacities and consolidation. There was lower lung, multifocal middle and bilateral peripheral lung involvement in the intermediate group. *7 patients depicted Covid-19 pneumonia of bilateral peripheral basal consolidation/ground glass haze. *Pattern of consolidation were in various shapes & sizes – inhomogenous, overlapping or patchy nodular opacity in peripheral distribution (majority cases) and smooth homogenous. *The Pakistani population showed a lot of middle lobe involvement which should be included in classical chest X-ray of Covid-19 which can help in future studies for a bigger scale. *Interstitial pneumonitis, drug induced pneumonitis and pulmonary edema can lead to Covid-19 pneumonia. *Pleural effusion and lymph adenopathy were uncommon in Pakistani population

"Korean J Radiol. 2020 Apr"	"Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea"	Yoon.S et al, Korea https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7082662/	" To study a report on the chest radiographic and computed tomography (CT) findings of the 2019 novel coronavirus disease (COVID-19) pneumonia in Korea"	***9 Covid-19** positive patients, median age-54 years. *Parenchymal abnormalities were observed in 8 baseline chest CT and one follow up CT scan with findings of Covid-19 pneumonia. *5 point scale was used to detect abnormalities (1-normal, 2-patchy atelectasis/bronchial wall thickening, 3-focal alveolar consolidation, 4-multifocal consolidation, 5-diffuse alveolar consolidation) **Baseline chest radiographs-** *5/9 patients depicted abnormalities in chest radiograph {Severity scores}-2-one patient, 3-two patients, 4-one patient, 5-one patient. *Chest CT helped us to remove artifact of GGO & post-inflammatory focal atelectasis in grade 2 & 3 lesions which was breast tissue. *Therefore, 3/9 were confirmed with chest abnormality related to Covid-19 *1/3 patients had single nodular opacity in the left lower lung zone. *50% of the opacities were found in lower lung zones. *80% of the opacities were located in the peripheral region of the lungs. **Chest CT findings-** *9 patients were identified with 77 lung parenchymal lesions(8/9 had bilateral lung parenchymal abnormalities) *Lower lobe was the most frequently involved lobe (8 patients) *Left upper and lower lobes were affected in 6 patients *Out of 77 lesions-39% were patchy, 13% confluent and 48% were nodular *The peripheral lung was involved in 78% of the lesions *The posterior region of the lung was involved in 67% of the lesions. *Patchy and confluent lesions were formed as consolidative lesions and mixed GGO in 50% cases, pure GGO lesions in 35%, lesion with crazy-paving appearance in 10% cases and consolidation in 5%.
"European Radiology 2020 Feb"	"Initial CT findings and temporal changes in patients	Pan.Y et al, China https://link.springer.com/article/1	"To observe the imaging characteristics of the novel coronavirus pneumonia."	*63 Covid-19 positive patients, mean age-44.9±15.2 years *44.4% patients (28 patients) depicted that number of affected lobes in the lungs were 5.

	with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China"	0.1007/s00330-020-06731-x		*Single GGO was visible in some patients at an early stage *85.7% of the patients (54 patients) progressed with increasing GGO enlarged & consolidated and fibrous stripes. While solid nodules increased & enlarged mainly distributed in the middle & outer zone of lung. *Common manifestations of new coronavirus- • Patchy/punctate ground glass opacities • Patchy consolidation in sub-plural region.
"American Journal of Roentgenology July 2020"	"Clinical Features and Chest CT Manifestations of Coronavirus Disease 2019 (COVID-19) in a Single-Center Study in Shanghai, China"	Cheng.Z et al, China https://www.ajronline.org/doi/full/10.2214/AJR.20.22959	"To assess the clinical features and CT manifestations of COVID-19 by comparing patients with COVID-19 pneumonia with patients with non–COVID-19 pneumonia who presented at a fever observation department in Shanghai, China."	*11 Covid-19 positive patients , 22 patients with non-Covid-19 pneumonia ***Clinical Findings-** *The median platelet count & leukocyte count in Covid-19 positive patients were lower as compared to pneumonia patients. *More Covid-19 positive patients suffered from muscle ache as compared to pneumonia patients. ***CT Findings-** *All Covid-19 positive patients depicted GGO (100%) majorly located in the peripheral zone and 90.9% in pneumonia patients. *Mixed GGO was detected in 63.6% Covid-19 positive patients and 72.7% in pneumonia patients. *Covid-19 positive patients had higher median number of affected lung lobes (5>3.5) and segments (15>9) as compared to pneumonia patients. *In Covid-19 positive patients air bronchogram was seen more frequently as compared to pneumonia patients (72.7%>27.3%) *In Covid-19 patients reticular patterns were seen more frequently as compared to pneumonia patients (81.8%>22.7%) *In 2 Covid-19 positive patients with mixed GGO or pure GGO the shape of the GGO was round or oval and not patchy.

<table>
<tr>
<td>“Invest Radiol. 2020 Mar”</td>
<td>“Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes”</td>
<td>Xiong.Y et al, China https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147282/</td>
<td>“To quantify the severity of COVID-19 infection on high-resolution chest computed tomography (CT) and to determine its relationship with clinical parameters”</td>
<td>*42 Covid-19 positive patients
*The lesion size of lungs was graded as (0-nothing, 1-diameter<1cm, 2-diameter 1 to <3cm, 3-diameter 3cm to <50% of the lobe, 4- 50% to 100% of the lobe)
* Severity of opacification was calculated by summing up 5 lobar scores.
*The change in score of follow up & initial CT was used to analyse change in opacifications over time.
*INITIAL CT-
*From the initial CT a conclusion could be drawn that 10/42 patients had opacities in 1 lobe & 2 or more lobes were affected in 32/42 patients.
*Majority of the patients (38/42) had lesions in the lower lobes.
*The most vulnerable lobe was left lower lobe with 34/42 patients affected by it & the least affected lobe being the right middle lobe (26/42 patients)
*Majority of the patients (25/42) had the peripheral and central region of the lung affected.
*Multiple or single GGO were visible in the initial CT
*More than half of the total patients(23/42) showed consolidation along with air bronchogram (14/42 patients), pleural effusion (5/42 patients) and interstitial thickening (17/42 patients).
*Sum score of lesion size ranged between 1-17 (8.8±5.2)
*Follow up CT-
*83% of the cases showed change or increase in opacifications with single GGO being progressed to multiple GGO.
*The follow up CT showed that more cases developed fibrous stripes, air bronchograms, pleural effusion, interstitial thickening and consolidation.
*The lungs of severely affected patients showed “white lungs” due to diffuse lesions in both the lungs.
*The sum score of lesion size increased to 3-20 (13.2±4.8)
*The total opacification size started reducing in the 18th – 22nd day from illness onset.</td>
</tr>
<tr>
<td></td>
<td>“Detection of coronavirus Disease (COVID-</td>
<td>Sethy.P et al, India https://www.researchgate.net/profile/Prabira_Sethy</td>
<td>“To detect Covid-19 disease with the help of</td>
<td>*Two dataset were created-
<table>
<tr><td>DATASET 1</td><td>DATASET 2</td></tr>
<tr><td>25 Covid-19 positive chest X-ray images</td><td>133 Covid-19 positive chest X-ray</td></tr>
</table>
</td>
</tr>
</table>

	19) based on Deep Features”	/publication/340049850_corona_paperedited/links/5e7449eb299bf1c76a200b48/corona-paperedited.pdf	deep features in X-rays”	25 Covid-19 negative chest X-ray images (pneumonia)	images (including MERS,SARS,ARDS) 133 Covid-19 negative chest X-ray Images (pneumonia) ***CNN (**Convolutional neural network)-Helps in identifying corona positive as a classification task. ***SVM (**Support vector machine)-Helps in classifying deep features derived from deep models(AlexNet, GoogleNet, ResNet18, ResNet50, ResNet101 etc) ***The SVM classifier uses the deep features obtained by each CNN network. ***After the classification has been performed, performance of all the classification models are measured. ***Deep features of CNN models are obtained from a layer and we get a feature vector. ***The feature vector are given to SVM classifier for disease identification purpose. ***The performance of each CNN model was measured in terms of accuracy, specificity, sensitivity, F1 score and false positive rate. ***ResNet50 with SVM model performed better than the rest 10 models in terms of accuracy, specificity, F1 score and lowest false positive rate in terms of Covid-19 detection. Accuracy-95.38% False positive rate-65.29% Specificity- 93.47% F1 score- 95.52%

"Comput Biol Med. 2020 Jun"	"Application of deep learning technique to manage COVID-19 in routine clinical practice using CT images: Results of 10 convolutional neural networks"	Ardakani.A et al, Iran https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190523/	"To detect Covid-19 disease with the help of deep features in CT scan"	*108 Covid-19 positive patients, 86 with other atypical and viral pneumonia *Important chest computed tomography findings- GGO, multifocal patchy consolidation and peripheral distribution of crazy paving pattern *10 different CNN models were used to examine Covid-19 infection and to differentiate them from other pneumonia cases *The deep learning models were able to differentiate between Covid-19 and other pneumonia cases with high accuracy. *ResNet-101 and Xception gave the best results. *Xception network did not have best sensitivity but had the best performance in differentiating Covid-19 and non-Covid-19 infections. *ResNet-101 had higher sensitivity, accuracy and NPV but lower specificity and PPV as compared to Xception. *A method with highest sensitivity to diagnose Covid-19 patients is desirable. *ResNet-101 is better than Xception due to its highest sensitivity and accuracy. *ResNet-101 has proved to be the best CNN model when compared with other models.
"American Journal of Roentgenology May 2020"	"Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome"	Hosseiny.M et al, USA https://www.ajronline.org/doi/10.2214/AJR.20.22969	"To review the lessons from imaging studies obtained during severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks"	***Imaging characteristics of SARS-*** *80% of the patients showed abnormalities in their chest radiographs. *Baseline radiographs in SARS showed unilateral disease along with peripheral distribution and opacity in the region of lower lung zone. *Majority of the patients in their follow up radiograph developed multifocal consolidation in the period of 6-12 days (involving one or both lungs) *Amongst 1/4th patients the opacity remained focal and unilateral. *CT helped to detect GGO and consolidation. *Involvement in four or more lung zones and consolidation progressed 12 days after the onset of symptoms. ***Imaging characteristics of MERS-*** *83% of the patients showed abnormalities in their chest radiograph. *The most common finding was opacities in the lower lung zones.

				*****Disease progressed in upper lobes and peripheral zone. *****CT showed GGO in the peripheral or basilar lung zone. *****Pleural effusion, interlobular septal thickening isolated consolidation was seen in 20-33% patients.

METHODOLOGY

The report is based on the descriptive secondary research data. Previous articles regarding history of X-ray and CT scan, SARS, MERS, Covid-19 and history of coronavirus were also reviewed. Articles pertaining to imaging findings in X-ray, CT scan and the application of deep learning features to detect Covid-19

DISCUSSION

Sars-Cov-2, MERS-Cov and Sars-Cov are part of the same family of virus i.e family of Coronaviridae. SARS infected more than 8000 people and lead to 774 deaths. MERS infected more than 2500 people and lead to 866 deaths. On 30th January 2020, the outbreak of Covid-19 was declared to be a public health emergency of international concern by the World Health Organization (WHO). As of 11th July 2020 Covid-19 has infected more than 12,848,622 cases and more than 563,521 deaths. Sars-Cov-2 can be easily transmitted through air droplets and person to person contact so it proves to be a huge threat to global public health. All these virus are zoonotic virus i.e the source of infections are wild animals- bats or camels. Covid-19 has a lower mortality rate (5.3%) as compared to SARS (9.6%) and MERS (34.3%) but higher reproduction rate (5.7) when compared with SARS (0.3-4.1), MERS (0.3-1.3) which resulted to a high death toll (n=567,766). Shortness of breath, cough, fever, fatigue, muscle pain were some of the common signs and symptoms of patients suffering from Covid-19, SARS or MERS.A study from China showed that patients suffering from Covid-19 had lower levels of platelet and leukocyte count as compared to other pneumonia patients. If the patient is older than 60 years or suffering from any comorbidity and is immunosuppressed then they have a higher chance of death. Radiological findings in SARS & MERS- More than 80% of the cases in SARS and MERS showed abnormalities in their chest radiograph. Opacities were found in the lower lung zone along with the presence of GGO and consolidation in the lungs. Involvement in four or more lung zones and consolidation progressed 12 days after the onset of symptoms in SARS. Pleural effusion, interlobular septal thickening isolated consolidation was seen in 20-33% patients in MERS.

Chest X-ray and portable chest X-ray are the best alternate method for testing Covid-19 patients. Portable chest X-ray gets an advantage when compared with an OPD X-ray room or CT scan room because decontamination measures cannot be followed there. The study in Pakistan found that 93% of the cases depicted abnormal chest radiograph and 33.3% cases had single nodular opacity in the left lower lung zone in the study of Korea. We derived from the study of Pakistan that 63% of the cases had lower lung, multifocal middle and bilateral peripheral lung involvement. The cases of Korea showed that 50% of the opacities were found in the lower lung zone and 80% of the opacities were located in the peripheral region of the lungs. Therefore, chest radiographs were able to depict that the peripheral region and lower lung zones were affected. In the study of Pakistan, 7 patients depicted Covid-19 pneumonia of ground glass haze/ bilateral peripheral basal consolidation. Pattern of consolidation were in different shapes and sizes- inhomogenous, overlapping or patchy nodular opacity. Interstitial pneumonitis, drug induced pneumonitis and pulmonary edema can lead to Covid-19 pneumonia. Middle lobe involvement should be included in classical chest X-ray of Covid-19 which can help in future studies for a bigger scale. Chest X-ray images showed GGO, peripheral

consolidation, single nodular consolidation and air bronchograms. Chest X-ray has a low sensitivity and differentiating between Covid-19 or other viral pneumonia is difficult based in chest X-ray.

CT scan is an important screening tool for detecting Covid-19 due to its convenience and high sensitivity. The studies from China and Korea helped us to understand that the lobes of the lungs were severely affected in Covid-19 patients. In some cases left upper lobe, lower lobes or else all the lobes of the lungs were affected. 44.4% of the cases in the study of China showed that all of the lobes of lungs were affected. Covid-19 positive patients had higher median number of affected lung lobes (5>3.5) and segments (15>9) as compared to pneumonia patients in a study of China. CT scan helped us to identify the number of lesions and location of the lesion present in Covid-19 positive patients. The study of Korea helped us to identify 9 patients with 77 lung parenchymal lesions (8/9 had bilateral lung parenchymal abnormalities). Out of 77 lesions-39% were patchy, 13% confluent and 48% were nodular. The peripheral lung was involved in 78% of the lesions. The posterior region of the lung was involved in 67% of the lesions. A study conducted in China showed that majority of the patients (38/42) had lesions in the lower lobes. The follow up CT depicted that the lungs of severely affected patients showed “white lungs” due to diffuse lesions in both the lungs. Ground glass opacity or GGO is considered as an important Chest CT finding in Covid-19 positive patients which indicates filling of air spaces in the lungs by fluids. In a study of China, mixed GGO was seen in 50% cases and pure GGO lesions in 35% cases. In another study from China, single GGO was visible in some patients at an early stage. 85.7% of the patients (54 patients) progressed with increasing GGO enlarged & consolidated and fibrous stripes. In a study of China where 11 Covid-19 positive patients were compared with 22 pneumonia patients- all Covid-19 positive patients depicted GGO (100%) majorly located in the peripheral zone and 90.9% in pneumonia patients. Mixed GGO was detected in 63.6% Covid-19 positive patients and 72.7% in pneumonia patients. In two Covid-19 positive patients with mixed GGO or pure GGO the shape of the GGO was round or oval and not patchy. The follow up CT of 42 Covid-19 positive patients in a study of China showed that 83% of the cases showed change or increase in opacifications with single GGO being progressed to multiple GGO. Consolidation in lungs appears in the chest CT of Covid-19 positive patients. More than half of the total patients (23/42) showed consolidation in the initial CT and even more cases developed consolidation in the follow-up CT in the sub pleural region in a study conducted in China. Chest CT scan helped us to identify that the most vulnerable/affected region for a Covid-19 positive patient is the lower region of the lungs- majority of the opacities were visible in this region. CT scan is given more preference for higher sensitivity than X-ray, early detection of disease but poses challenges related to infection control- airflow, decontamination measures and ventilation.

When deep learning models are applied with X-ray and CT images it enables the radiologist to give more accurate results. A radiologist requires time to read an X-ray or CT image. Therefore, by developing a deep learning model which identifies Covid-19 positive cases with more precision and it saves a lot of time during the pandemic when people are sick around the world. The different CNN models helps in identifying corona positive as a classification task. SVM helps in classifying deep features derived from deep models. In a study conducted in India, ResNet50 with SVM model gave the best results for X-rays in terms of accuracy, specificity, F1 score and lowest false positive rate in of Covid-19 detection (Accuracy-95.38%, False positive rate-65.29%, Specificity- 93.47%, F1 score- 95.52%). In a study from Iran, 10 CNN models were used to examine Covid-19 infection from CT images. The deep learning models were able to differentiate between Covid-19 and other pneumonia cases with high accuracy. ResNet-101 proved to be the best CNN model for detecting Covid-19 from CT images when compared with other models due to its highest sensitivity and accuracy (sensitivity-100%, accuracy-99.51%).

CONCLUSION

Fast and accurate detection of Covid-19 is need of the hour right now. Chest X-ray and chest CT are crucial in diagnosing Covid-19 patients and to keep a check on the health of the lungs. An imaging pattern of opacity with pure/mixed GGO, consolidation and lesions majorly affecting the lower region and the peripheral region of the lungs. With the progression of the disease many patients were diagnosed with multiple affected lobes of the lung. The two deep learning models- ResNet-50 and ResNet-101 have helped in deriving accurate results and saves a lot of time. Therefore, X-ray and CT scans when combined with deep learning models can prove to be an effective diagnostic tool in covid-19.

REFERENCES

[1] https://www.radiologyinfo.org/en/submenu.cfm?pg=xray

[2] https://www.radiologyinfo.org/en/info.cfm?pg=bodyct

[3] https://www.medscape.com/answers/2500114-197399/what-is-coronavirus

[4] https://www.who.int/health-topics/coronavirus#tab=tab_1

https://emedicine.medscape.com/article/2500114-overview#a1

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html

https://en.wikipedia.org/wiki/Severe_acute_respiratory_syndrome

https://en.wikipedia.org/wiki/Middle_East_respiratory_syndrome

https://www.radiologyinfo.org/en/info.cfm?pg=bodyct

https://www.medscape.com/answers/2500114-197431/what-is-the-incubation-period-for-coronavirus-disease-2019-covid-19

https://www.nde-ed.org/EducationResources/CommunityCollege/Radiography/Introduction/history.htm

https://www.imaginis.com/ct-scan/brief-history-of-ct

https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7132650&blobtype=pdf

Durrani, M., Haq, I. U., Kalsoom, U., & Yousaf, A. (2020). Chest X-rays findings in COVID 19 patients at a University Teaching Hospital - A descriptive study. *Pakistan journal of medical sciences*, *36*(COVID19-S4), S22–S26. https://doi.org/10.12669/pjms.36.COVID19-S4.2778

Yoon, S. H., Lee, K. H., Kim, J. Y., Lee, Y. K., Ko, H., Kim, K. H., Park, C. M., & Kim, Y. H. (2020). Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. *Korean journal of radiology*, *21*(4), 494–500. https://doi.org/10.3348/kjr.2020.0132

Pan, Y., Guan, H., Zhou, S. *et al.* 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* 30**,** 3306–3309 (2020). https://doi.org/10.1007/s00330-020-06731-x

Cheng Z, Lu Y, Cao Q et al. Clinical features and chest CT manifestations of coronavirus disease 2019 (COVID-19) in a single-center study in Shanghai, China. AJR Am J Roentgenol 2020. doi: 10.2214/AJR.20.22959

Xiong, Y., Sun, D., Liu, Y., Fan, Y., Zhao, L., Li, X., & Zhu, W. (2020). Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Investigative radiology*, *55*(6), 332–339. https://doi.org/10.1097/RLI.0000000000000674

Sethy.P , Behera.S(2020). Detection of coronavirus Disease (COVID-19) based on Deep Features. 10.20944/preprints202003.0300.v1

Ardakani, A. A., Kanafi, A. R., Acharya, U. R., Khadem, N., & Mohammadi, A. (2020). Application of deep learning technique to manage COVID-19 in routine clinical practice using CT images: Results of 10 convolutional neural networks. *Computers in biology and medicine*, *121*, 103795. https://doi.org/10.1016/j.compbiomed.2020.103795

Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology perspective of coronavirus disease 2019 (COVID-19): lessons from severe acute respiratory syndrome and Middle East Respiratory Syndrome. *AJR Am J Roentgenol*. 2020;1-5:1-5. doi:10.2214/AJR.20.22969

[5]https://en.wikipedia.org/wiki/2002%E2%80%932004_SARS_outbreak#/media/File:2003_Probable_cases_of_SARS_-_Worldwide.svg

[6] https://www.covid19india.org/

SUMMER TRAINING REPORT-PART 2

Pharmaceutical and Medical Device Innovations

This course gives an in-depth view of two domains which are one of the most crucial parts of the healthcare industry-

1) Pharmaceutical Industry
2) Medical Device Industry

The course provides complete knowledge about the drug/device development process, challenges faced during development, defining a market space and new technologies, the share of pharmaceutical and medical device purchase across the globe by different countries. It covers the concept behind patent protection, components of branded drug cost, difference between prescription & OTC drugs as well as different classes of medical devices. It also provides information on FDA(Food and Drug Administration)&NICE(National Institute of Health and Care Excellence) the governing bodies responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices of USA(United States of America) and UK (United Kingdom) respectively.

This course will cover the components of branded drug cost comprising of production and quality control, research and development, administration, distribution and marketing. The trends in cancer drug. How reimbursement decision making takes place in the UK (United Kingdom) and what is the British criteria for cancer drug payment. In addition, the course will discuss the different kinds of reimbursement coding- CPT, ICD-10, HCPCS-II. How codes are used, how payment is made to healthcare providers and how USA(United States of America) device public reimbursement takes place. We also get to learn about the top-notch of healthcare industry in the world that is the French healthcare sector and how reimbursement takes place over there.

Objectives

- Students will gain an understanding of current trends in the drug development, the importance of personalized medicine and what is the healthcare dollar.
- Students will study about Medicare and different parts of healthcare coverage in Medicare.

- Students will gain an understanding about the FDA approval required for the medical devices and the three different classification of medical devices.
- The course teaches the learner about the difference between drugs and devices. How are devices similar to drugs, limitations and benefits of convergence of the two industries.

Course Contents

Week 1	The Pharmaceutical Industry: Bench Science to Bedside	1) Overview; Pharmaceutical Industry: Trends in Drug Development 2) Pharmaceuticals: From Bench to Bedside 3) Pharmaceutical Industry: Drug Development Challenges 4) Pharmaceutical Industry: Intellectual Property 5) Pharmaceutical Industry: FDA 6) Pharmaceutical Industry: Global Regulatory & Harmonization 7) Pharmaceutical Reimbursement: US Market 8) Pharmaceutical Reimbursement: Public Insurance Market 9) Pharmaceutical Reimbursement: Overseas US Market	
Week 2	Pharmaceutical Market Deployment & Management	1) Defining a Market Space 2) Who are your customers? 3) Who or what Influences your Customers? 4) Early Competitors in Brand Space 5) Global Space Competitors 6) Generic and Over the Counter (OTC) 7) Trends in Cancer Drugs 8) British Criteria for Cancer Drug Payment 9) U.S. Criteria for Cancer Drug Payment	
Week 3	The Medical Device Industry: Bench Science to Bedside	1) Medical Device Industry: Regulatory Basics 2) Device Failure 3) MD and Pharma Convergence 4) Reimbursement Coding 5) Payment to Healthcare Providers 6) MD Industry: Reimbursement Strategy 7) U.S. Device Public Reimbursement 8) U.S. Device Private Insurer Reimbursement 9) Medical Device Reimbursement Outside U.S	
Week 4	Medical Device Market Deployment & Management	1) Market Space 2) Innovation Pipeline & Valuation 3) Global Partnerships 4) Device Competitor Analysis 5) Global Competitor Analysis 6) The 510k: Friend or Foe? 7) Go to Market 8) Managing Market Share 9) Keeping the Product Fresh and Safe in the Long Run	

Learning Methodology:

The course is available on Coursera platform. The lectures were delivered via videos with the help PowerPoint presentations as resource. After the completion of each week a test had to be attempted with more than 80% score. When the course ended, a final assignment had to be submitted which signified the completion of the course.

Key Learnings

- **Personalized medicine** are a set of drugs which are customized according to a person's unique genetic makeup, circumstance of their demographics.
- Personalized medicine components in **cancer treatment** can be transformative to **reduce long term hospital calls, physician cost** for the benefit that comes from **prescription drugs**.
- A generic drug is a prescription medication made of the same chemical material as a medicatio n initially covered by chemical patents.The active chemical material is the same, and output is assumed to be similar to the medical profile of generics.
- In 2014, nearly **9 out of 10** US prescriptions are filled with generics.
  So, one **advantage** of generics is that the **price** can be **a lot cheaper** than that would be otherwise for say a brand-name medication though.
- **Pre-discovery** is a period when **thousands of compounds** are tested for a drug, it takes three to six years. There's an **Investigational New Drug (IND)** form, that's submitted in to the FDA to let them know what's going on. The FDA's **primary objective** in **reviewing** an IND is to look at all the phases of investigation, to assure the **safety and rights of its subjects**.
  Clinical trials then commence and then methodically being narrowing down to, say, **five compounds**. The new drug application is then submitted and then, finally the drug is reviewed then put into **large scale manufacturing** with post-marketing surveillance. **A very long process** and to get one **blockbuster drug**.
- When researchers are involved in a drug discovery it comprises of- **58% pharmaceutical company, 24% university and 18% bio-tech company.**
- It's very important to **file your patent**, as soon as you have an idea get the patent because chances are your patent will not necessarily get approved for quite some time. So, patent can take **three to five years** and then once all that's done you can then start the **FDA approval process** which takes another **ten to twelve years**. So, in the **twenty year window until patent expiration** you only have **four to six years to sell your product.**
- **Prescription drug** price **decreases** significantly over time. Generic medicine usually costs up to 80 per cent less than brand medicine.
- **70% of HIV patients** receive treatment with **low cost** generic drugs of assured quality from **India**. Due to market competition from Indian companies, first line AIDS treatment regimes now cost approx**. $90-130/patient/year**, a **quarter the price of the R&D companies** charge in US and European markets.
- Before a **physician** can in the US can legally prescribe a drug for a patient, the drug must be approved by the **FDA**. When the FDA approves a drug, it is approved for **certain conditions or indications**. No matter what the drug's label says a physician can **legally prescribe** the drug for any reason, this is called **prescribing the drug off-label**. If the product is considered to be a **supplement** instead of a **drug**, it **does not** need to be approved by the **FDA**.
- If the drug is approved by the FDA for particular indication, the drug is given a NDC**.**
- Private insurance are of 2 types-
  (A)Group Insurance (is often offered by employers)-Group insurance can be- **(i)Fully Insured**-The employer or association who provides the health insurance charges an insurance company a fee and is responsible for making all claims to the insured members to file them.

(ii)Self Insured- The employer or association that provides the health plan is their own insurer and is responsible for covering all claims made by insured members.**(B)Individual Insurance** (is typically purchased on your own)

- **Medicare** is a government health benefit program for both citizens and legal residents of the US who have resided in this country for a continuous period of **five years** who either
  - are age 65 and older or
  -are under age 65
- There are different parts to Medicare-
  (i) Medicare **Part A** pays for **in-hospital treatment**.
  (ii)Medicare **Part B** pays **for out-patient** services such as **physician office visits** and some **medications**.
  (iii)Medicare **Part D**(a new optional program) provides **prescription drug coverage**, through private insurance plans, to Medicare beneficiaries who enrol in a plan.
  (iv)Medicare **Part C**(Advantage plan) which **combines** part **A,B and D.**
- **Biosimilar** is a biological medicinal product which is very similar to another biological medicine already approved. **Biosimilars** in the US and French market have been rapidly increasing.
- Another major difference is that generics are copies of synthetic drugs, whereas biosimilars are modeled on drugs which use living organisms as important ingredients.
- But many analysts expect the two will share a vital commonality and that, like generics, biosim ilars can significantly lower the cost of biologic drugs.
- A **drug** is an article intended for use in man or other animals for the diagnosis , cure, mitigatio n,treatment or prevention of disease intended to affect the structure or any function of a man or other animal's body.
- **Brand-name drugs** are those drugs that are always **on patent** where the pharmaceutical company trying to get their **full profits.**
- **Q) What is driving expenditure growth?**
  Expenditure=Price x Quantity 3/4th increase due to expanded use and switching to new and more effective drug. 1/4th due to price increases.
- **Four primary reasons by MIT-** (1) Getting addicted to drugs (2)Expansion of insurance coverage for pharmaceuticals (3)New Product Innovation (4) Aggressive Marketing
- **Q) Who are the principals?**
  - Manufacturers
  - Wholesalers
  - Retailers
  - Other agents in pharmaceuticals- Insurers, Employers, Pharmaceutical benefit managers, Consumers, Regulators
- **Q) Who are your customers?**
  - Patients- users of the products
  - Providers- physicians or pharmacists
- Role of pharmaceutical representative-
  - Product education
  - Address contract/pricing issues
  - Serve as a mode of communication to home office departments: medical affairs, product quality, marketing, clinical studies
  - Meet customer needs
- **Medical care representatives** works in hospital/academic medical center environment and has the key responsibility to identify and develop academic thought leaders
- Key influence methods for customers-
  - Advertising
    -TV (since 1997)

-Magazines
-Internet
- Physicians
- Alternate providers
-Pharmacists
-Nurse
- Science
- Popular culture
-TV
-Movies

- **Q) What is a branded (original) drug?**
  Drugs marketed by the company that manufactures them with a specific brand name, usually the company that develops them and patents them.
- **Q) Who discovers drugs?**
  - Identify biological target- biology
  - Prioritize/validate target- pharmacology and chemistry
  - Identify and optimize lead molecules- chemistry/pharmacology
  - Preclinical studies – chemistry/pharmacology/toxicology
  - Formulation- pharmaceutical sciences
  - Clinical evaluation- medicine
  - Manufacture- chemical engineer
- **GETTING A DRUG INTO THE MARKET**
  - Disease target-possible drug candidates
    -Pre-clinical testing; R&D (1-3 years)
  - Toxicology (to find out any adverse drug reactions)
  - Clinical R&D (2-10 years; average-5 years)
    -Phase 1 (healthy volunteers)
    -Phase 2 (small patient group)
    -Phase 3(larger patient group)
  - Regulatory approval (2-10 years)
  - Market
  - Phase 4 – long term marketing
- **Pharmaceutical companies** incur **a loss of billions of dollars** after their **patent expiration.**
- Different kinds of patent protection-
  - Specific delivery method
  - Specific product/molecule
  - Specific manufacturing process
  - Specific medical indication
  - Specific combination

Q) What is a generic drug?

A clone of an initial drug for which the expiry enables manufacturing and distribution if the patent protects the innovator product.

- The three main concepts of quality, safety and efficacy apply to generic in the manufacture of generic drugs in the same manner as they do to the innovator product.
- An average of **14 years and 800 million dollars** is spent on each discovery that reaches the public. A **copy** can be produced in **1 year for less than 1 million dollars**.
- Difference between generic and branded drug-
  - Quality of raw material used

- Method of synthesis
- Packaging, stability and evaluation

- As per the FDA a generic drug must-
    - contain the same active ingredient as revolutionary medicine
    - be identical in strength, dosage form and routine of administration
    - have the same use indications
    - be bio-equivalent
    - meet the same batch strength, pureness and quality requirements
    - be developed in compliance with the same strict GMP standards required for innovator product s
- Only on the advice of an accredited health provider, such as a physician, are prescription medications a vailable.
- **Non-prescription drugs (over-the-counter or OTC)** are available on request and do not require approval by health professional.
- People who need medical attention are increasingly rejecting the production of medicinal products
- Move for more natural forms of treatment to prevent unwanted side effects
- Natural healing continues to expand and become a major business
- Food is being used as a substitute for medication. For example - (1**) dark chocolate** is being pegged as the next new thing to **combat blood pressure** and **prevent heart problems**. **(2)cherries and berries** are being used by many elderly people with **mild arthritis** rather than joint medication.
- Label details regulated by the FDA- name of the product, identity, active ingredients, amount, supplier, what to use, how to use, what to look for, potential drug reactions if medication should not be used any longer.
- There has been a **164% increase** in the **price of cancer drugs** in **USA** in the last **7 years**.
- Decision(reimbursement) making in the UK-
    - NICE covers England and Wales
    - SMC covers NHS Scotland
    - HPSS in Northern Ireland considers NICE guidance
- Cost-per-QALY indicates the value in UK as per NICE
- Government regulation and medical devices-
    - The role of the government is the most important difference between marketing non-medical and medical technologies.
    - Government agencies determine approval and training.
    - Need to understand the process and the bureaucratic details in order to plan the tech assessment (it is the gathering and analysing of information on the performance of a technology.
    - Once a stage in the development/regulatory process has passed, the chance to gather important information may be lost forever.
- How does a new technology make it to the market?
    - Obtain a patent
    - Regulatory approval from the FDA that the new device or drug may be marketed.
    - Payers must agree to cover the drug/device/procedure.
    - Providers must be persuaded to use the innovation.
- It takes from 6 months to 2 years for the patent office to grant a patent. Patent life is 20 years from the application date.
- "A medical device is any device intended to be used for medical purposes. Medical devices benefit patients by helping health care providers diagnose and treat patients and helping patients overcome sickness or disease, improving their quality of life."
- Medical devices classes-
    - Class 1- products are lowest risk and most are not subjected to pre-market review.

- Class 2- products pose either low or moderate risk.
- Class 3- technologies generally are higher risk, breakthrough products are not similar to currently marketed products.

- Approximately 30% of all medical devices are placed in class 1, 60% in class 2 and 10% in class 3.
- How devices are different from drugs?
  - Drugs are metabolized and devices are not.
  - Pharmaceutical market is larger than medical devices market.
  - Reimbursement policies are different.
  - The consumer is different.
- How devices are similar to drugs?
  - Both are heavily subsidized by government funded research.
  - Both require FDA approval to survive.
  - Government reimbursement policy is a critical factor in their marketing strategy.
  - Both need to make cost-savings or cost-effectiveness argument when seeking FDA and insurance reimbursement approval.
- Coding systems used for reimbursement-
  - **Current procedural terminology**- used to describe procedures for which a physician, hospital outpatient department and laboratory are paid.
  - **International classification of diseases**- 1) Procedure code- used to describe the inpatient procedures for which a hospital is paid. 2) Diagnosis code- describes the medical reason for why a service/procedure is provided.
  - **Healthcare common procedural coding system II-** used to describe products, eg-medical equipment, devices and some procedures.
- How codes are used-
  - Used on insurance claims forms to link services/supplies/devices/drugs to payment.
  - Establish medical necessity.
  - Define coverage and payment rates.
  - Analyze healthcare utilization which can affect future payment rates and Medicare audit reviews.
  - Tracks diseases.
- How do hospitals get paid?
  There are two classes of hospital procedures/treatments-
  - Inpatient- Hospitals get a fixed payment from Medicare for each admission independent of length of stay or cost incurred by the hospital.
  - Outpatient- Paid according to the ambulatory payment classification (APC) system.
- Medicare coverage decision-
  - Medicare decides what to cover
  - Usually specify that a procedure is covered if certain conditions are present.
  - Standard is “reasonable and necessary” but recent evidence suggests that the cost effective standard might be relevant.
- How to manage risk in business?
  - Minimizing cannibalization-
    A company that approaches plain products must ensure that it has a deep understanding of pre mium customers and the features they prefer, and that their value offers do not meet these need s.
  - Defending against competition-
    In order to achieve a competitive edge in value goods, premium businesses must rapidly reach scale.

- Remaining flexible- In certain main accounts , those who pursue a lean sales model that need to provide additional clinical help or more versatile inventory assistance.