Chapter 1- Introduction

Since the emergence of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2) in Wuhan, China, in 2019, and the World Health Organization (WHO) declaring it a pandemic on March 11, 2020, the world has been witnessing a major public health crisis in the form of death, social and economic disaster (Saxena *et al.*, 2021). After SARSCoV and Middle East Respiratory Syndrome Coronavirus (MERSCoV), this is the third coronavirus outbreak in the previous 20 years (Padmaprakash *et al.*, 2021). This disease has so far afflicted 220 countries and territories around the world, resulting in about 191 million cases and 4 million fatalities where some countries have been hit harder than others, with Europe taking the brunt of the damage. In Asia, around 59 million cases have been documented, with India reporting the highest number of cases. Bangladesh has seen an increase in cases as well, with the total number of confirmed cases exceeding 1 million (Worldometer, 2021). The country was placed under lockdown with a graded entry and exit plan to counteract the pandemic's rapid spread. It also increased its readiness, with a major project being the establishment of COVID 19 hospitals throughout the country for in-patient care.

Because of the location and pneumonia symptoms, the disease was initially dubbed "Wuhan pneumonia" by the media (Y. C. Liu *et al.*, 2020). It belongs to the beta corona virus family, positive sense, enveloped, non-segmented, single stranded RNA virus with the largest genome of all the RNA viruses identified so far (De Groot *et al.*, 2013; Shen *et al.*, 2020). It is very similar to bat coronaviruses where bats are considered to be the primary source. However, the 2019-nCoV's origin is still being explored (Nanshan Chen *et al.*, 2020). "The spike glycoproteins that radiate from the virus envelope of the spherical particles are responsible for the characteristic crown-like appearance of coronaviruses" (Milne-Price *et al.*, 2014).

The SARSCoV2 receptor, also known as human angiotensin converting enzyme 2 (hACE2), is the host factor that causes illness in several organs (Batlle *et al.*, 2020). Individuals with diabetes, hypertension, cancer, chronic kidney disease, cardiovascular diseases and Chronic Obstructive Pulmonary Disease (COPD) are particularly vulnerable to this virus (G. Li *et al.*, 2020). Furthermore, persons with a weak or compromised immune system, such as pregnant women, newborns and the elderly are more likely to contract SARSCoV2 (Chang *et al.*, 2020). Besides, in quantitative blood cell abnormalities, a bunch of laboratory indicators like LDH (Lactate Dehydrogenase), ESR (Erythrocyte Sedimentation Rate), CRP (C-Reactive Protein), D-dimer, Ferritin, Procalcitonin (PCT), Interleukin-6 (IL-6) were investigated and found to be linked with poor outcomes of Covid-19 patient (Zeng *et al., 2020)*.

Thrombocytopenia, leukocytosis with neutrophilia as well as lymphopenia and biochemical parameters like increased bilirubin, serum urea, creatinine and hepatic enzymes, are all linked to a higher risk of death in patients hospitalized to the intensive care unit (ICU) (Chan *et al.*, 2020; J. Liu *et al.*, 2020). However, excellent diagnostic value of chest CT (Computed Tomography) plays an important role in treatment plan by showing the severity of infection through imaging pattern and area of lung involvement (Ramanathan *et al.*, 2020; Tenda *et al.*, 2020). Moreover, higher levels of serum amyloid A (SAA) have been linked to COVID-19 development and could be used as a biomarker to track disease progression (Pieri *et al.*, 2021). Studies have found no difference in the levels of IL-6, SAA, ESR, CRP; hence these findings are contentious (Chen *et al.*, 2020; Wu *et al.*, 2020; Zhang *et al.*, 2020).

Infection with the virus causes a number of clinical symptoms. The most notable one is an ARDS-like picture with a cytokine storm, which can lead to serious complications such as respiratory failure, cardiac arrest, acute renal injury and death (Kwok *et al.*, 2021). However, the majority of infected people are asymptomatic or have minor flu symptoms (fever, cough, sore throat etc.), which can be treated at home or in isolation centers to prevent transmission. Those with moderate to severe symptoms will require institutional treatment, which may include oxygen therapy, intensive care and ventilation support (Aylward & Liang, 2020).

Despite the fact that, the majority of patients are asymptomatic or just mildly symptomatic, the condition is putting a burden on healthcare services due to its large number of patients and the need for expensive intensive care. As COVID-19 represents a spectrum of clinical severity ranged from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death (Goh *et al.*, 2020; Guan *et al.*, 2020); therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures of reducing mortality.

Currently no approved drug is available for the treatment of COVID-19 (Hossein-khannazer *et al.*, 2021). For mild to moderate cases of infection, patients are treated with daily analgesics and antipyretics for symptomatic relief. Anti-inflammatory agent like dexamethasone, anti-viral drug such as remdesivir and a recombinant humanized anti-IL-6 receptor monoclonal antibody named tocilizumab - are being applied for critical cases. As supportive treatment, fluid therapy and oxygen support are typically given to Covid-19 patients (National Institutes of Health, 2021; Wei *et al.*, 2021). These treatment options are varying depending on the stage of the sickness and disease manifestations, and may have limited effects based on the severity and duration of the illness (EUROPEAN MEDICINES AGENCY, 2021).

Significant differences in management may often be observed globally because the clinical profile and outcomes of this disease vary from country to country. Bangladesh follows the recommendations made by Directorate General of Health services (DGHS) for Covid-19 treatment. On the basis of their oxygen saturation, sickness duration and co-morbidities mild patients are treated symptomatically, while moderate cases receive anti-thrombolytics (Enoxaparin), antivirals (Remdesivir) and steroids (DGHS, 2021). In order to prevent infections in critically ill patients, antibiotics are also provided as a prophylaxis. Tocilizumab is kept reserved for certain patients whose condition causes rapid respiratory decompensation. Other medications including Ivermectin, Bevacizumab, Baricitinib; and convalescent plasma therapy can only be administered as part of clinical trials because there is insufficient data on their effectiveness.

While physicians in the country are repurposing different drugs to treat cases of COVID- 19 with no clear remedies for the disease, research institutes, both within the country and abroad in collaboration with biotech companies have already identified strategies to produce effective vaccines using viral proteins. These are RNA-based vaccines (developed by Moderna, Pfizer/BioNTech), DNA-based vaccines (Inovio Pharmaceuticals), non-replicating viral vector vaccines (Oxford/AstraZeneca, CanSino/Beijing, Gamaleya, Janssen and serum institute of India); and inactivated vaccines (Sinopharm and Sinovac). Seven of these vaccines are currently approved in Bangladesh (Sattar, 2021). Since social distancing and personal protective measures such as frequent hand washing and use of face masks and gloves were unable to hinder the transmission of this deadly virus, vaccination has become an excellent option to limit disease spread.

At this critical stage of pandemic widespread vaccination is believed to be crucial not only for controlling the transmission, infection and consequent death risks associated with COVID-19, but also for achieving herd immunity. On 27th January 2021, Bangladesh government initiated the public vaccination program against COVID-19 with priority for first responders such as physicians, nurses and other healthcare workers (Ahamad *et al.*, 2021). Covishield, also known as ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), was distributed by the government of Bangladesh for immunization against COVID-19 over the country.

COVID-19 vaccines are highly effective and greatly reducing the risk of severe illness, hospitalization, and death from COVID-19. Although COVID-19 vaccines work well to prevent severe illness and death among those exposed to the virus, a small percentage of fully vaccinated people will still get COVID-19 infection. As the vaccine offers strong protection against the most serious outcomes of COVID-19, increasing vaccination rates is key to limiting severe COVID-19 cases and saving lives (Health, 2021). Many factors affecting the outcome of the disease in which COVID-19 vaccine is one of them which need to be explored thoroughly.

According to earlier research, patients who require intensive care are typically older and male. Additionally, about 40% of these patients have comorbid problems such as diabetes, heart disease, hypertension, asthma and other chronic illnesses like liver or renal diseases (Anwar *et al.*, 2020; Wynants *et al.*, 2020). About 5% COVID-19 patients, who are severe or critically ill require admission to an intensive care unit (WHO, 2020). However, the high mortality rate of critically sick patients is due to a lack of conventional healthcare services, particularly ICU assistance.

COVID-19 patients of higher age and with pre-existing chronic health conditions may require immediate hospitalization and intensive care (Anwar *et al.*, 2020). Bangladesh has a very negligible number of ICU beds as compared to its vast population. Chattogram, the port city of Bangladesh, one of the most crowded economic and trading centers, is classified as a high-risk zone for SARS-CoV-2 contact transmission (Rana *et al.*, 2020). On April 3, 2020, Chattogram city witnessed its first 2 COVID-19 positive cases, followed by the first death on 9 April.

Despite being the prime economic zone of the country, the condition is even worse in Chattogram in terms of ICU facilities. In order to meet the needs of ICU facilities and plan for a potential next wave of COVID-19, it is crucial for health and government authorities to obtain information on the clinical features and consequences of COVID-19 in critically sick cases. Similar epidemiological studies have already been carried out sampling COVID-19 patients admitted in the ICU in China, Iran, Pakistan, India, Greece, and the United States in order to discern COVID-19's clinical implications on patients who had to be admitted in the ICU. There is little robust data available from Bangladesh. Very few single-center, small studies are available from Dhaka. Experts can use the insights from these investigations to better identify the precise management and follow-up medical procedures (Cummings *et al.*, 2020; Halvatsiotis *et al.*, 2020; Poussardin *et al.*, 2020).

To the best of our knowledge, no prior study from Chattogram as well as Bangladesh has been able to present a thorough clinical profile of both vaccinated and non-vaccinated COVID-19 patients admitted in ICU by looking at the full suite of patients' characteristics, clinical presentation, diagnostic test results, treatment options, complications and health outcomes.

In order to paint a more comprehensive picture of the severe clinical manifestations of COVID-19, this study will look into the epidemiological and clinical characteristics, disease severity, treatment, and clinical outcomes of critical COVID-19 cases in Chattogram. This will enable Bangladesh's healthcare system to approach COVID-19 with more flexibility.

Objectives:

- To study the socio-demographic status of COVID-19 patients admitted in ICU.
- To investigate the comorbidities and clinicopathological parameters of COVID-19 patients admitted in ICU.
- To assess the association between clinicopathological findings with the outcome (death) among COVID-19 patients admitted in ICU.

Chapter 2- Literature Review

2.1 Background

The Novel Coronavirus 2019, was first reported in Wuhan, China in late December 2019. The outbreak was declared a public health emergency of international concern in January 2020 and on March 11, 2020; the outbreak was declared as global pandemic. The virus has been named SARS-CoV-2 and the disease it causes has become known as coronavirus disease 2019 (COVID-19).

Coronavirus is a positive-sense RNA virus that is classified under the order Nidovirales, family Coronaviridae and the subfamily Orthocoronavirinae (Yan *et al.*, 2020). These viruses can be characterized by the appearance of spikes that protrude on their surface and they have the capability to infect specific vertebrates. On the basis of serological and genomic properties, the subfamily is further divided into 4 Genera: *Alpha, Beta, Gamma* and *Deltacoronavirus.* The *Betacoronavirus* can additionally be split into four lineages: A, B, C and D. SARS-CoV-2 that has recently been identified has been classified as subgenus *Sarbecovirus* of the lineage B (Letko *et al.*, 2020) Owing to its widespread availability, large genetic diversity and frequent recombination of the different coronavirus species, along with the increased time humans spend with animals, coronaviruses can occasionally mutate to infect human hosts (Zhu *et al.*, 2020b).

From different coronavirus species identified so far, there are 6 species that can infect human hosts (also called HCoV). Depending on the lineage of the coronavirus species as well as the immunocompromised nature of the infected human host, the symptoms can vary from mild illness to severe respiratory distress or even death (Fung & Liu, 2019). Although the new coronavirus SARS-CoV-2 was first discovered in a cluster of patients who reported symptoms of pneumonia of unknown cause to local health facilities in Wuhan, China, in early December 2019, the original source of this virus is yet unclear (Yan *et al.*, 2020).

Several notable variants of SARS-CoV-2 emerged throughout 2020. As of December 2021, there are 5 dominant variants of SARS-CoV-2 spreading among global populations: the Alpha variant (B.1.1.7, formerly called the UK variant), first found in London and Kent, the Beta variant (B.1.351, formerly called the South Africa variant), the Gamma variant (P.1, formerly called the Brazil variant), the Delta variant (B.1.617.2, formerly called the India variant), and the Omicron variant (B.1.1.529), which had spread to 57 countries as of 7 December (WHO, 2021).

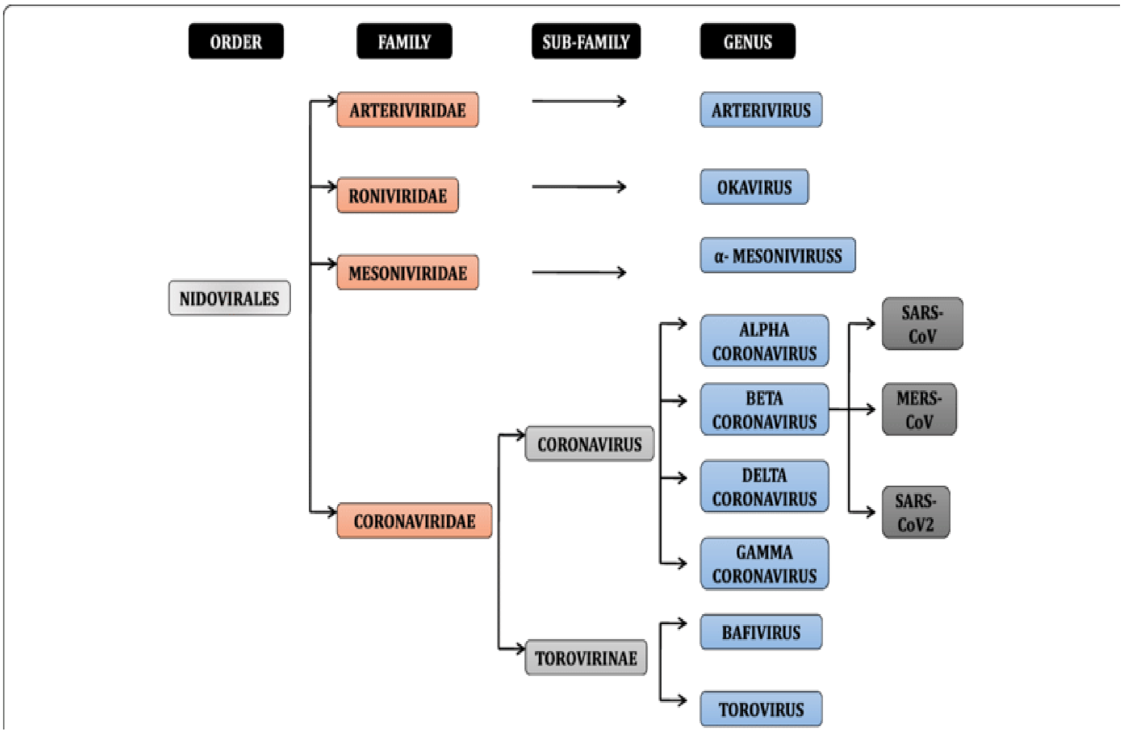

Figure 1: Classification of coronaviruses
Source: (Shaikh *et al.*, 2020)

2.2 SARS-CoV-2 structure

The SARS-CoV-2 is a β-coronavirus which is an enveloped non-segmented and positive-sense RNA virus (Zhu *et al.*, 2020b). They are divided in to 4 Genera, namely α-, β-, γ-, and δ- CoV. While α- and β- CoV are able to infect mammals, γ-, and δ- CoV tend to infect birds. Formerly, 6 CoVs have been identified to cause infections in humans among which α-CoVs HCoV-229E and HCoV-NL63; and β-CoVs HCoV-HKU1 and HCoV-OC43 caused mild respiratory symptoms with mild pathogenicity (Yin & Wunderink, 2018). The coronavirus core particle is further surrounded by an outer membrane envelope made of lipids (fats) with proteins inserted. A key set of the proteins in the outer membrane project out from the particle and are known as spike proteins (S). It is these proteins which are recognized by receptor proteins on the host cells which will be infected (King *et al.*, 2020).

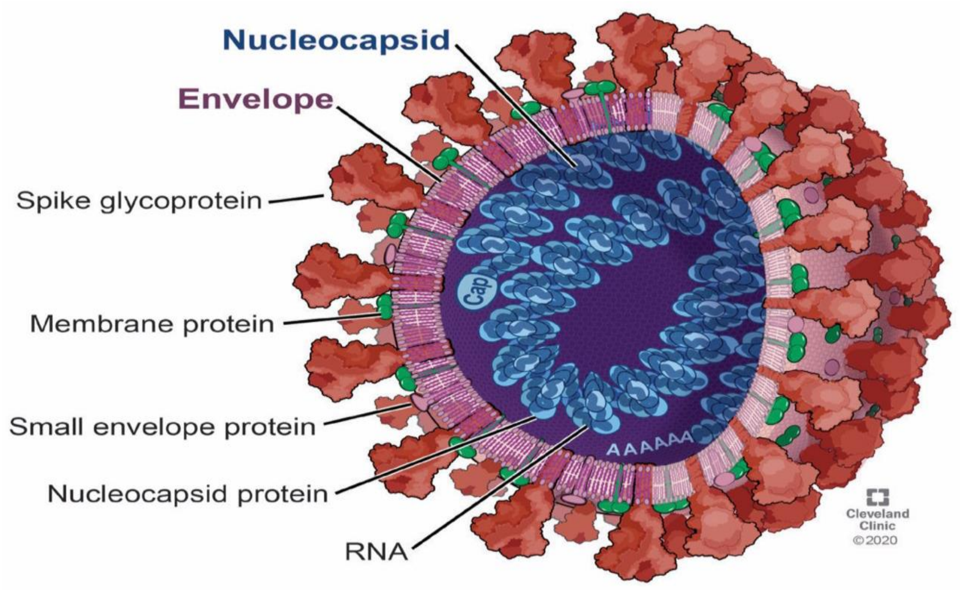

Figure 2- Structure of SARS-CoV-2
Source:(Bergmann & Silverman, 2020)

2.3 Mode of spread

SARS-CoV-2 is a novel severe acute respiratory syndrome coronavirus. It was first isolated from 3 people of Shenzhen with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan. All structural features of the novel SARS-CoV-2 virus particle occur in related coronaviruses in nature. Outside the human body, the virus is destroyed by household soap, which bursts its protective bubble. SARS-CoV-2 is closely related to the original SARS-CoV (Zhu *et al.*, 2020b).

It is thought to have an animal (zoonotic) origin. On emergence of cluster of pneumonia cases in Wuhan, China in 2019, suspicion of yet another outbreak was revealed. All confirmed cases of SARS-CoV-2 from 1st to 20th January 2020 that were admitted to Wuhan Jinyintan Hospital were studied and 49% of the subjects had some form of previous exposure to Hunan Seafood Wholesale Market which had live-animals on sale (Y. Chen *et al.*, 2020). Further study of the viral genome showed that this species of coronavirus was 96.2% identical to a bat coronavirus. Other studies done on genome sequencing of SARS-CoV-2 also showed similar results suggesting bats to be the primary reservoirs for the virus. However, the intermediate host in passing the virus to humans hosts still remains unclear since several animal species were present at the Wholesale Market (Jiang *et al.*, 2020).

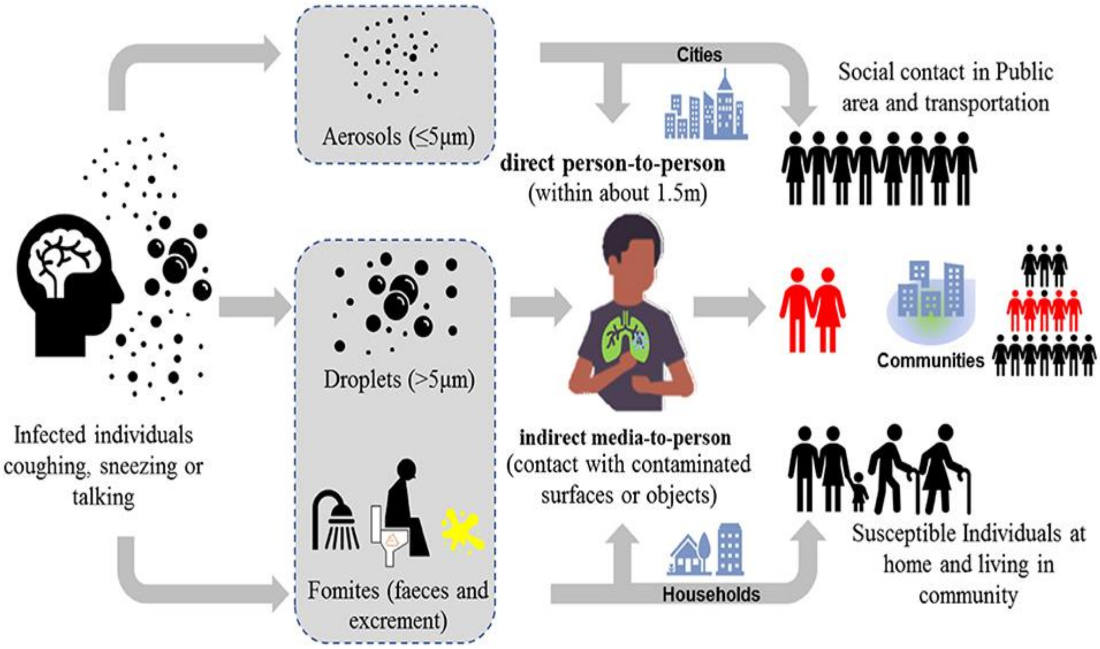

Figure 3- Mode of spread of Covid-19
Source: (Hu *et al.*, 2021)

Human to human transmission can easily occur between close contacts and multiple routes of transmission has been identified. Although the disease primarily spreads by respiratory droplets, respiratory secretions and direct contact, studies have reported the presence of this virus in fecal swabs as well as blood, suggesting that infection could spread in this way also (Zhang *et al.*, 2020). Since ACE 2 receptors are present in abundance in the lung alveoli as well as the enterocytes of the small intestine (Hamming *et al.*, 2004), routes of infection as well as disease manifestation can be understood from this.

2.4 Pathogenesis and host response

A vast variety of body cells and systems are susceptible to infection by the SARS-CoV-2 virus. COVID-19 is most known for affecting the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs). The lungs are the organs most affected by COVID-19 because the virus accesses host cells via the receptor for the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant on the surface of type II alveolar cells of the lungs. The virus uses a special surface glycoprotein called a "spike" to connect to the ACE2 receptor and enter the host cell (Harrison *et al.* 2020).

2.4.1 Cellular response

From patient to patient, COVID-19's cellular response differs. Patients with minor symptoms as well as those who have recovered from severe illness display a typical immune response to the virus. Patients with deadly severe COVID-19, however, proceeded through 3 stages: hypofunction or normal, hyperactivation, and finally anergy. In the end, these people succumb to the viral illness and pass away (X. Zhou & Ye, 2021).

In the early stages of COVID-19, the total number of white blood cells in peripheral blood is either normal or decreased (National Health Commission of the People's Republic of China, 2020). T and B lymphocytes are cells that are important indicators for detecting immune function. These T lymphocytes are further classified into 2 important subsets: CD3+ CD4+ T lymphocytes and CD3+ CD8+ T lymphocytes. CD4+ T cells can differentiate into a range of helper and effector cell types, as well as have the ability to indicate B cells, assist CD8+ T cells, have direct antiviral activity, recruit innate cells and promote tissue repair. On the other hand, CD8+ T cells can kill infected cells and affect the activation of the immune response.

As another important component, B lymphocytes play a role in humoral immunity by secreting antibodies. In normal viral infections, the lymphocyte counts increase in response to the infection. However, contrary to this, in Covid-19 infections, the lymphocyte counts decrease with increasing severity of the disease (Schulte-Schrepping *et al.*, 2020). The number of T lymphocytes in severe patients were lower than in mild patients, and much lower in deceased patients. Even the B lymphocytes are decreased with patients with severe illness having lower counts than those with mild illness (X. Zhou & Ye, 2021).

Due to the initial local respiratory SARS-CoV-2 infection, the number of circulating innate immune cells in the blood, including natural killer cells, monocytes, neutrophils and dendritic cells change. Patients with severe COVID-19 have higher neutrophil counts in their blood, whereas dendritic cells, the body's most effective full-time antigen-presenting cells (APCs) have lower counts as the disease gets worse.

2.4.2 Cytokine response

Cytokines are produced by numerous immune cells including the macrophages, dendritic cells, natural killer cells and the T and B lymphocytes. During an innate immune response to any viral infection, there are pattern recognition receptors (PRRs) that recognize the different molecular structures distinctive to the invading virus. These structures are referred to as pathogen associated molecular patterns (PAMPs). When PAMPs bind to PRRs an inflammatory response is triggered against the invading virus. This results in activation of various signaling pathways and later transcription factors which induce gene expression responsible for production of several products involved in the host's immune response to the virus. Among these are the genes encoding several pro-inflammatory cytokines. This sequence of events results in the recruitment of leukocytes and plasma proteins to the site of infection where they perform many effector functions that help to combat the triggering infection (Thompson *et al.*, 2011). Although exaggeration of the host's immune system can lead to severe disease (Braciale & Hahn, 2013).

Three important pro-inflammatory cytokines of the innate immune response are IL-1, TNF- α, and IL-6. When there is an acute increase in circulating levels of different pro-inflammatory cytokines such as IL-6, IL-1, TNF- α, and interferon, it causes a sudden influx of various immune cells such as macrophages, neutrophils, and T cells into the infection site. This is called “cytokine storm” and it has a destructive effect on human tissue due to damage of vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure and finally death. Lung injury is one consequence of the cytokine storm that can easily progress into acute respiratory distress syndrome (ARDS) (Shimizu, 2019). This leads to low oxygen saturation level and hence is a major cause of death in COVID-19 patients.

Multiple studies suggest that some patients with COVID-19 suffer from a cytokine storm (CS). One study analyzed the cytokine levels of 41 COVID-19 confirmed cases with pneumonia and found elevated levels of IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α, and VEGF in these patients as compared to healthy adults (Huang *et al.*, 2020). One specific marker that was significantly raised in severe cases of COVID-19 was IL-6. Multiples studies showed this specific finding where raised IL-6 levels were significantly higher in cases who died (Ruan *et al.*, 2020) or when comparing between mild and severe cases (Y. Chen *et al.*, 2020).

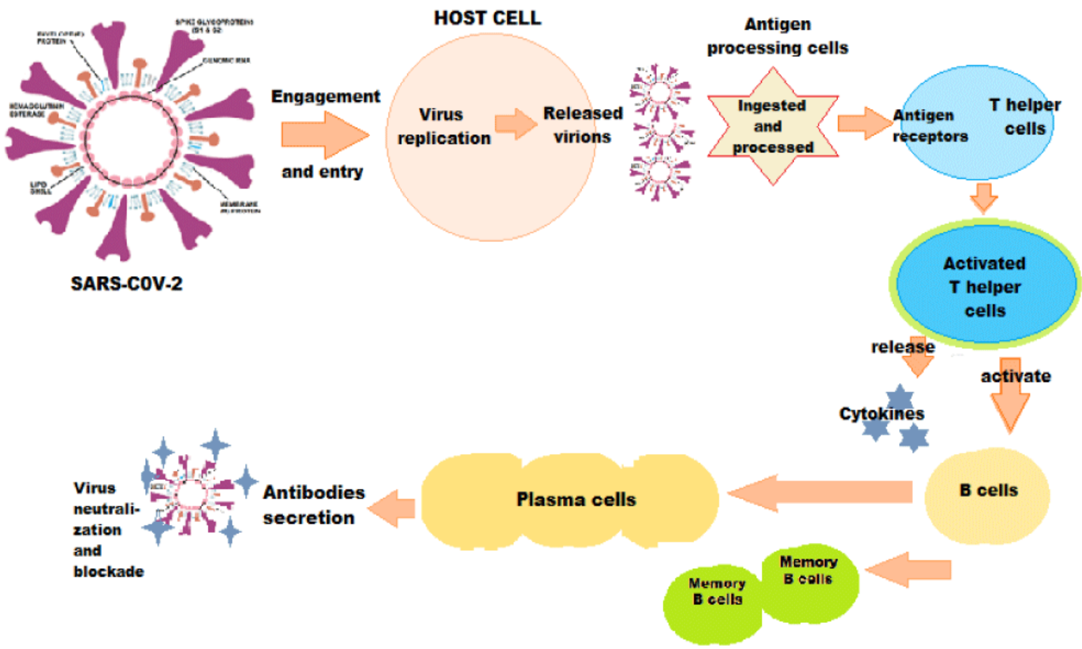

Figure 4: Immune response against SARS-CoV-2

Source: (Vinod, 2021)

CS has been reported in many viral infections including the previous two coronavirus infections-SARS and MERS. Both pro-inflammatory and anti-inflammatory cytokines are raised in the serum of patients with CS. Hence in COVID-19 patients, along with antiviral therapy, anti-inflammatory therapies that reduce cytokine responses are necessary (Ragab *et al.*, 2020).

2.4.3 Antibody response

Generally, antibodies to SARS-CoV-2 are not detectable in the very early stages of infection. One study by (Liu *et al.*, 2020) showed that anti-SARS-CoV-2 IgM antibodies were detectable from the 4^{th} day of illness onset which increased over time and peaked at 20 days after which it gradually declined and was markedly reduced after 28 days.

Anti-SARS-CoV-2 specific IgG antibodies were detectable from day 7 of illness onset and peaked at approximately 25 days of illness onset and the levels were still maintained high 4 weeks later. In the early stages of infection, no significant difference was observed in serum IgG levels between mild and severe cases, but after 15 days of disease onset, both IgM and IgG levels were vigorously raised in cases of severe illness. Furthermore, the timing in developing IgM and IgG antibodies varied greatly among patients and this could be associated with age and comorbidities of the patient.

2.5 Clinical Features and diagnosis of Covid-19

The clinical features of SARS-CoV-2 is highly variable from person to person with asymptomatic cases to acute respiratory distress syndrome and multi-organ failure. From various studies of laboratory confirmed cases, the common clinical manifestations included fever, cough, fatigue, production of sputum, shortness of breath and sore throat. Additionally, some patients may present with gastrointestinal symptoms like diarrhea and vomiting. Elderly patients and patients with comorbidities such as diabetes, hypertension, COPD, cardiovascular diseases, etc. rapidly develop acute respiratory distress syndrome, shock, metabolic acidosis and coagulation dysfunction leading to death (Huang *et al.*, 2020).

As Covid-19 showed both symptomatic and asymptomatic infections, the global prevalence of SARS-CoV-2 infection remains unknown. Confirmed cases for symptomatic patients and the SARS-CoV-2 infection can manifest as an asymptomatic or mild disease. Similar to other viral infections, appropriate collection of specimens is key to proper diagnosis of the disease. Acceptable specimens include upper respiratory tract specimens, lower respiratory tract specimens, stool specimens, whole blood specimens, and serum specimens, with respiratory tract specimens being the most frequent. There are many different types of tests that can be used to diagnose COVID-19. The testing of SARS-CoV-2 is grouped into molecular testing and serology testing.

The molecular testing includes nucleic acid amplification test (NAAT) such as real-time reverse-transcription polymerase chain reaction (rRT-PCR). The unique sequence RNA of the virus including nucleocapsid (N), envelope (E), spike protein (S), and RNA-dependent RNA-polymerase (RdRP) genes are targeted to analyze using rRT-PCR. The nucleotide sequence of the viral RNA molecules is not found in human DNA or RNA sequences. The test for the presence of the virus, thus, tests for the presence of the viral RNA sequences in tissue samples. This test requires adequate supplies of two enzymes and the primers, specialized instruments for running the reaction at elevated temperatures, and trained personnel (Lai *et al.*, 2021).

However, the clinical manifestations of COVID-19 include both respiratory and extra-respiratory signs and symptoms and can range from an asymptomatic mild disease to severe disease or acute respiratory tract infections. Therefore, misdiagnosis of COVID-19 can occur in patients without a characteristic presentation, even for 14 asymptomatic and mild infections, and in places where rRT-PCR is unavailable. These issues could limit our understanding of the extent of SARS-CoV-2 infection and further affect the implementation of infection control and prevention policies. The use of a serological test to detect antiSARS-CoV-2 antibodies could be a better way to estimate the burden of SARS-CoV-2 infection than the PCR method, and help improve understanding of the associated epidemiology (Lai *et al.*, 2020).

- **Antibody (Serology) Test**: A more traditional test for virus infection is the presence of antibodies that bind to the virus. Such tests identify individuals who are now healthy but have previously been infected. Antibody tests require a small drop of blood and are much more rapid than the current nucleotide sequencing tests. It detects antibodies that are made by the immune system in response to a threat, such as a specific virus. It is not used to diagnose active infection. The serology testing of COVID-19 is not targeting the virus itself but the antibodies such as immunoglobulin M (IgM) and immunoglobulin G (IgG) induced following viral infection. These immunoglobulins are serological testing markers after the patient has early (3–6 days after exposure to the virus, IgM) and late virus infections (after 8 days, IgG) response respectively (Rai *et al.*, 2021)**.**

The absence and/or poor implementation of both RT-PCR and antibody-based tests early in the outbreak is the main cause of failure to control the outbreak particularly after the experiences of the SARS and MERS viruses. Currently, the routine clinical diagnosis of Covid-19 is based primarily on epidemiological history, clinical manifestations, and is confirmed by various laboratory methods such as CT scan, nucleic acid amplification test amplification test (NAAT), and serological techniques. For early screening and diagnosis, specimens like nasopharyngeal swabs, oropharyngeal swabs, bronchoalveolar lavage fluid, bronchial aspirate, sputum, and blood are generally recommended.

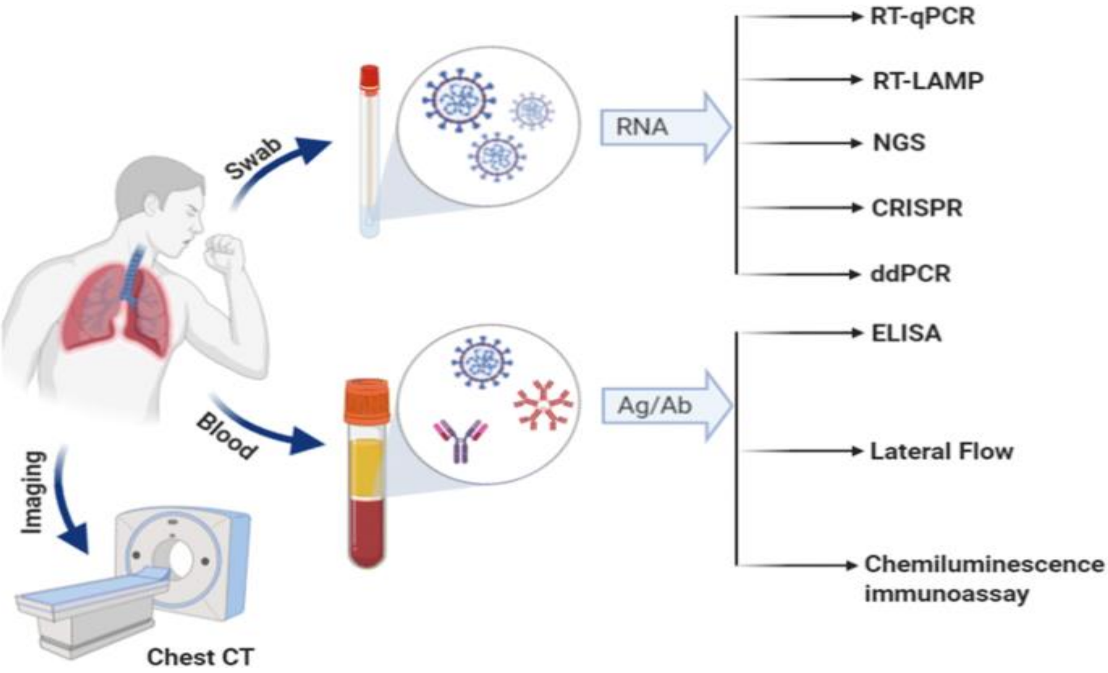

Figure 5: Various analytical methods available for SARS-CoV-2 detection

Source- (Rai *et al.*, 2021)

On 3 February 2020, in Japan, 712 (19.2%) of 3711 passengers and crew had tested positive to COVID-19. At the time of testing, 331 (46.5%) of those with positive results were asymptomatic. Although the later infected persons reported no symptoms, some actually had subclinical changes in their lungs. When computed tomography scans for 76 of these persons were examined, 54% showed lung opacities (Oran & Topol, 2020)

Another study revealed the proportion of asymptomatic persons as 17.9%. the proportion of asymptomatic individuals appears to be 16.1% (35/218) before 13 February, 25.6% (73/285) on 15 February, 31.2% (111/355) on 16 February, 39.9%

(181/454) on 17 February, 45.4% (246/542) on 18 February, 50.6% (314/621) on 19 February and 50.5% (320/634) on 20 February (Mizumoto *et al.*, 2020)

On 28 March, an initial case of COVID-19 was diagnosed with a positive test result at a homeless shelter in downtown of Los Angeles, California. After a cluster of symptomatic persons was identified early in the week of 20 April, the shelter was closed to new occupants and testing was started for current occupants. As of 22 April, 43 (24.2%) of 178 completed tests were positive for SARS-CoV-2 and 27 (63.8%) of the persons who tested positive were asymptomatic (Chou, 2020).

Widespread outbreaks of COVID-19 in the correctional facilities of several states of USA have led to large-scale screening programs. According to research by Reuters journalists, as of 25 April 2020, SARS-CoV-2 test results that include data on symptom status were available for 4693 inmates in the state prison systems of Arkansas, North Carolina, Ohio, and Virginia. Among these inmates, 3277 (69.8%) tested positive, of whom 3146 (96%) had no symptoms at the time of testing (So and Smith, 2020).

2.6 Covid-19 in Critical Care

The requirement of intensive care among COVID-19 hospitalized patients varies between countries from 5% to 32% (Halaçli *et al.*, 2020). In some studies, it has been reported that many factors including age, sex, and comorbidities are associated with the severity of disease and ICU admission (Phua *et al.*, 2020). According to these studies, severe disease is accompanied by acute kidney injury, acute respiratory distress syndrome (ARDS), myocarditis shock cardiac, and septic shock. Hence, ICU admission plays a crucial role in the care of COVID-19 patients and also is effective in decreasing the mortality rate (Rajani *et al.*, 2020).

Currently, as ICU resources are limited and typically more than 50% of its capacity is full under normal conditions therefore, in emergency conditions such as the COVID-19 pandemic we have to focus more on distinguishing critical patients to save more ICU capacity and classify ICU-needed from non-ICU-needed patients (Moghadas *et al.*, 2020).

2.6.1 ICU organization

In part of a pandemic plan of the country and hospitals, ICU beds should be organized as well as all devices, equipment, and personnel. Patients should be followed in an isolated room; necessary personnel protective equipment (PPE) should be provided and a dedicated team for COVID ICU should be organized. For this purpose, patient to nurse ratio could be 1:1, if possible. A stand-by clean medical team may also be considered. It is recommended to change the team that takes care of COVID-19 patients in every 14 days. Hereby, a wash-out period is provided. It is also suggested that health care workers should not work for longer than 12h a day in order to minimize risk of infection (Liew *et al.*, 2020).

It should be considered that the existing intensive care beds and organization may not be sufficient due to the pandemic. Potential solutions are expanding intensive care outside ICUs, like high-dependency units, general wards, post-anaesthesia care units, and even operating rooms. On the other hand, surging in the ICU capacity brings an incremental demand for equipment such as ventilators, consumable materials, therapeutics and as well as human force as healthcare workers (HCW). HCW who are currently working out of ICU should be systematically trained in terms of COVID-19 protocol for supporting ICU staff (Qiu *et al.*, 2020).

2.6.2 Infection control

To ensure proper infection control measures in the ICU are crucial. Contact and droplet isolation precautions should be undertaken (Grasselli, Zangrillo, *et al.*, 2020b). Faeco-oral transmission has also been reported (Phua *et al.*, 2020). Viral shedding is expected to be extremely high in critically ill patients. Interventions such as bag-valve-mask ventilation, noninvasive mechanical ventilation (NIMV), high flow nasal cannula oxygen (HFNO), nebulization and oro-tracheal intubation automatically bring high risk in terms of aerosol production. Expanded aerosol production might increase airborne transmission risk as well. That is why airborne isolation (with negative pressure) should ideally be implemented as soon as possible in a single room with negative pressure supply that should be provided at least >12 h/day (Wang *et al.*, 2020b). Fluid-resistant gown, two longer sleeved gloves to prevent exposure of the wrists with glove subsiding, eye glasses, full face shield, hair covers or hood, N95 mask and shoe worn are recommended for exposure to confirmed or suspected

COVID-19 patients. Disposable shoe covers might increase the risk of self-contamination during removal of protection clothing and should be avoided. All ICU team should wear hospital's scrubs which should not be worn outside the hospital (Y. H. Jin *et al.*, 2020).

2.6.3. Respiratory support

Hypoxemic respiratory failure should be recognized early. Despite conventional oxygen therapy, increased work of breathing and hypoxemia could become progressively worse. Supplemental oxygen should be given via low-flow O_2 delivery systems such as nasal cannula (1-6 L/min to provide FiO2 of 0.24–0.45), simple face mask (5–8 L/min to provide FiO_2 up to 0.50–0.60), nonrebreather masks with reservoir providing FiO_2 up to > 0.85 with 10–15 L/min oxygen, titrated according to SpO_2. Venturi and diffuser masks are suggested to be avoided. It should be remembered that FiO_2 > 0.60 for > 6 h might create O_2 toxicity. HFNO therapy and NIMV support may be applied in selected hypoxemic respiratory failure cases with proper PPE because of high risk of aerosol generation. When applying NIMV, a helmet mask may be used, applied with intensive care ventilators or dual-circuit ventilators; a viral/bacterial filter should be added to the circuit. NIMV should not be applied to patients whose secretions cannot be controlled; who have high aspiration risk, impaired mental status, cardiac complications and multiple organ failure; and who are hemodynamically unstable (Tran *et al.*, 2012).

Almost 10% of patients may require invasive mechanical ventilation. Endotracheal intubation should be applied by a trained and most experienced physician with a rapid sequential intubation protocol. Intubation with flexible bronchoscopy can be used in difficult intubation. Positive pressure ventilation should not be initiated before the endotracheal cuff is inflated and patients must be connected to mechanical ventilator directly without bag ventilation (Wax & Christian, 2020).

PEEP titration should be applied at pressures that will prevent atelectotraumas and over distention. In moderate (PaO2/FiO2 < 200) and severe (PaO2/FiO2 < 100) ARDS patients, high PEEP may be applied instead of low PEEP. Extracorporeal membrane oxygenation (ECMO) may be considered in patients with refractory hypoxemia despite lung-protective ventilation, and appropriate patients should be referred to experienced centres. ECMO is not a therapy that should be considered in case of a major pandemic regarding the appropriate allocation of resources (Maclaren *et al.*, 2020).

Dr. Gattinoni and his colleagues suggested that COVID-19 patients with respiratory failure have 2 phenotypes (Gattinoni *et al.*, 2020). Phenotype characterized by low elastance (high compliance), so called Type L, has low ventilator perfusion ratio, low lung weight, and low recruitability, whereas Type H, characterized by high elastance (low compliance) has high right-to-left shunt, high lung weight, and high recruitability. They recommend to increase FiO2 as a solution for hypoxemia for those who are not experiencing dyspnoea, in which Type L patient responds well. Early intubation may even cause transition to Type H phenotype. However, for intubated hypercapnic Type L patients, ventilation with more than 6 mL/kg up to 8–9 mL/kg does not bring risk of ventilator-associated lung injury.

2.6.4. Management of sepsis and shock

Due to lack of evidence, most of the recommendations are weak or as best practice statements regarding management of COVID-19 patients with shock. Dynamic parameters like skin temperature, capillary refilling time, and/or serum lactate measurement are suggested. Conservative fluid management is superior to liberal approach for acute resuscitation. Buffered/balanced crystalloids are preferred over unbalanced in the initial treatment. Hydroxyethyl starch is not suggested which is a strong recommendation. In addition, gelatins and dextran should not be used as well. Norepinephrine is the first-line vasoactive agent. Vasopressin and then adrenalin should be added as a second-line agent, over titrating norepinephrine dose, if target MAP cannot be achieved by norepinephrine alone (Arentz *et al.*, 2020a)

First hour sepsis bundle should be implemented as baseline lactate measurement and repeated if first measurement is >2 mmol/L; blood cultures before antibiotics and antimicrobial therapy should be started within 1h. If bacterial infection is suspected, appropriate empirical antimicrobial therapy should be initiated. The choice of antibiotic treatment is made according to the local epidemiological data and treatment guidelines of the patient’s clinical condition (Zhou *et al.*, 2020)

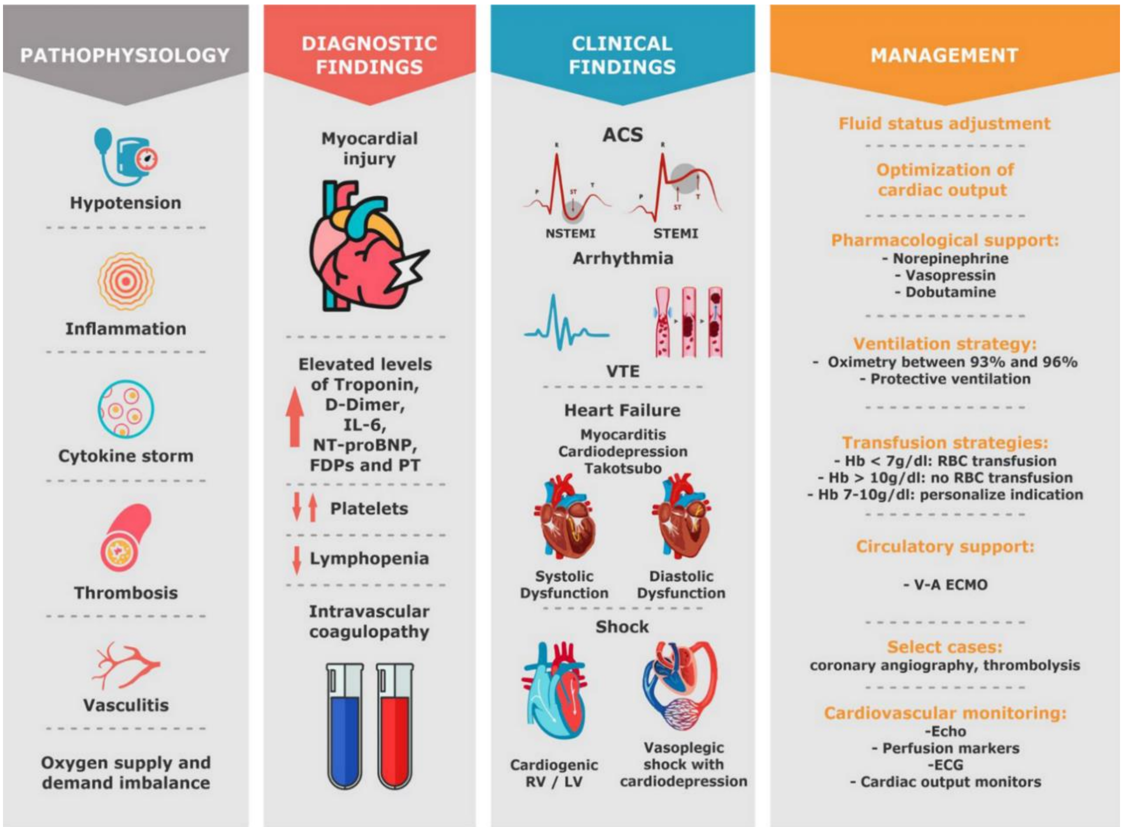

Figure 6: ICU management of Covid-19: a practical approach

Source: (Hajjar *et al.*, 2021)

In the critically ill patients, venous thromboembolism prophylaxis should be undertaken due to immobility. However, in COVID-19 patients, presence of hyper-coagulopathy is hypothesized and therefore, therapeutic anticoagulation and perhaps antiaggregant therapy should be considered in patients with no contraindications especially in patients with high d-dimer levels (Klok *et al.*, 2020).

2.6.5 Cardiopulmonary resuscitation (CPR)

In case of cardiac arrest, CPR should be managed with as few people as possible with PPE which must be worn by all members of the team before entering the room. No chest compressions or airway procedures should be done without full PPE use. CPR should be initiated by only chest compressions which could also be performed by automatic resuscitators and preoxygenation could be provided with nonrebreather face masks with reservoir to prevent aerosol contamination. All procedures should be debriefed after CPR for personal safety check and patient clinical evaluation (Qiu *et al.*, 2020).

2.6.6 Radiology

In the differential diagnosis of COVID-19 pneumonia, imaging tests should also be used in addition to the patient's history, clinical and laboratory findings and coronavirus specific diagnostic tests. Thorax computed tomography (CT) examination can be useful in diagnosis and can provide important clues in the initial evaluation of novel coronavirus pneumonia. Multiple patched ground-glass opacities in bilateral lobular style, with peripheral location, are reported as characteristic thorax CT findings of COVID-19 pneumonia (W. Yang *et al.*, 2020).

2.7 Profiles and outcomes of Critically Ill Patients

Available data suggest that 5-20% of patients with COVID-19 develop critical illness that is characterized primarily by the acute respiratory distress syndrome (ARDS) (Grasselli, Pesenti, *et al.*, 2020; Guan *et al.*, 2020a; Z. Wu & McGoogan, 2020a). Multiple factors related to demography, epidemiology, co-morbidity affect the clinical features and outcomes.

2.7.1 Demography and Epidemiology

A proportion of patients with coronavirus disease 2019 (COVID-19) can become critically ill due to either the development of acute respiratory distress syndrome (ARDS) or complications of the disease itself. Reports during the initial phase of the pandemic suggest that among those with COVID-19, up to 20 percent develop severe disease requiring hospitalization (Huang *et al.*, 2020; X. Yang *et al.*, 2020a; Young *et al.*, 2020). Among those who are hospitalized, up to one-quarter need intensive care unit (ICU) admission, representing approximately 5 to 8 percent of the total infected population (Grasselli, Pesenti, *et al.*, 2020; Richardson *et al.*, 2020; Z. Wu & McGoogan, 2020b).

Regarding demographics, respiratory tract infections are, in general, more severe in men and they tend to lead to higher mortality in men (Falagas *et al.*, 2007). Higher mortality for men was also observed during the severe acute respiratory syndrome (SARS) epidemic (G. M. Leung *et al.*, 2004). In a mixed group of patients with COVID-19 and SARS, Jin *et al.* found that sex and increased age were associated with more severe disease and mortality (Jin *et al.*, 2020). However, a systematic review on the association between demographic factors and different severity stages of COVID-19 is lacking.

Knowledge on the association between demographic factors and different severity stages of COVID-19 such as infection, severe disease, intensive care unit (ICU) admission and death may provide insight into the underlying pathophysiological mechanisms (immunity, coagulopathy and comorbidities). This knowledge may also guide clinical decision-making, especially when there is an impending shortage in healthcare resources such as ICU beds. Additionally, exploring demographic factors influencing Covid-19 outcomes may guide policymakers in, for instance, the prioritization of non-pharmaceutical interventions and screening (Ferguson *et al.*, 2020). These demographic factors may also be important for the design and interpretation of clinical trials on the efficacy of treatments as they could potentially be strong confounders.

A systematic review and meta-analysis of 59 studies published by BMJ showed that men had a higher risk for infection with COVID-19 than women (relative risk (RR) 1.08, 95% CI 1.03 to 1.12). When infected, they also had a higher risk for severe COVID-19 disease (RR 1.18, 95% CI 1.10 to 1.27), a higher need for intensive care (RR 1.38, 95% CI 1.09 to 1.74) and a higher risk of death (RR 1.50, 95% CI 1.18 to 1.91). The analyses also showed that patients aged 70 years and above have a higher infection risk (RR 1.65, 95% CI 1.50 to 1.81), a higher risk for severe COVID-19 disease (RR 2.05, 95% CI 1.27 to 3.32), a higher need for intensive care (RR 2.70, 95% CI 1.59 to 4.60) and a higher risk of death once infected (RR 3.61, 95% CI 2.70 to 4.84) compared with patients younger than 70 years (Pijls *et al.*, 2021). Although there were some limitations because most included studies (n=50) were from China involving Chinese patients with COVID-19 compared with only 9 studies from outside. Methodological limitations included the fact that disease severity was in most papers defined according to the clinical stages of COVID-19 issued by China and WHO interim guidance, but that was not always reported. Additionally, in some papers it was unclear whether severity was assessed on hospitalization or during follow-up. This is additionally complicated by the fact that referral policy to dedicated hospitals in China obscures the severity on initial admission. Therefore, it was not always clear whether an RR or OR was the most appropriate risk measure. RRs were used to obtain conservative estimates.

On May 19, 2022 a cohort study consisting of 787 Covid-19 patients from Keniya clearly showed that the risk of death from COVID-19 is high among older patients. Comorbidities were reported in 340 (43%), with cardiovascular disease, diabetes and HIV documented in 130 (17%), 116 (15%), 53 (7%), respectively. 90 (11%) were admitted to the Intensive Care Unit (ICU) for a mean of 11 days, 52 (7%) were ventilated with a mean of 10 days, 107 (14%) died. The risk of death increased with age (HR 1.57 (95% CI 1.13 to 2.19)) for persons >60 years compared with those <60 years old; having comorbidities (HR 2.34 (1.68 to 3.25)) and among men (HR 1.76 (1.27 to 2.44)) compared with women (Ombajo *et al.*, 2022).

2.7.2 Imaging and Laboratory Findings

Laboratory and imaging findings, as well as the factors associated with evolution of the disease and outcomes, constitute critical knowledge that should be carefully studied when a new infectious disease emerges.

The laboratory abnormalities predominantly found included hypoalbuminemia, elevated inflammatory markers, such as C-reactive protein, LDH, and ESR, among others. Also, lymphopenia is consistently present in more than 40% of the patients across eight studies with more than 500 patients. Moreover, other studies reported lymphopenia as a prominent finding in critical patients. Data from the 2002–2003 outbreak indicate that SARS may be associated with lymphopenia, leukopenia, and thrombocytopenia, elevated levels of LDH, alanine transaminase (ALT), AST, and creatine kinase (Lee *et al.*, 2003; Tsang *et al.*, 2003), but also, and not significantly seen, nor consistently reported, in COVID-19 studies and cases, with thrombocytopenia, mild hyponatremia, and hypokalemia. The frequency of lymphopenia found suggests that COVID-19 might act on lymphocytes, especially T lymphocytes, as does SARS-CoV, maybe including depletion of CD4 and CD8 cells (N. Chen *et al.*, 2020a). Virus particles spread through the respiratory mucosa, initially using the ACE2 receptor at ciliated bronchial epithelial cells, and then infect other cells (Rodriguez-Morales *et al.*, 2020). In most of the patient’s neutrophils were raised and lymphopenia was seen (Lado *et al.*, 2020). Yang *et al.* reported that more than 80% of the patients in critical setting had lymphocytopenia (X. Yang *et al.*, 2020a). However, the study conducted by Matthew *et al.* in New York found the older age, hypertension, chronic lung disease, and higher concentrations of interleukin-6 and d-dimer at admission to be independently associated with in-hospital mortality (Cummings, Baldwin, Abrams, Jacobson, *et al.*, 2020).

On 2020, a multicenter, retrospective, observational study in China stated that white blood cell counts were in the normal range with neutrophils predominant in intubated patients. 91.1% patients presented with lymphopenia where non-intubated patients, those intubated showed a significant decrease in lymphocyte counts [0.7 (0.5–0.9) vs. 0.4 (0.3–0.5), $p < 0.001$)]. Elevated levels of lactate dehydrogenase (LDH) (normal range, 109–255 U/L) were observed in 32 patients (71.1%). Additionally, intubated patients had higher levels of LDH than non-intubated patients [397.1 (342.2–523.8) vs. 285.3 (215.5–346.7), $p = 0.0012$]. Prothrombin time, D-dimer, troponin I, creatine kinase, serum creatinine, aspartate aminotransferase, lactate, procalcitonin, and potassium were significantly increased in intubated patients, whereas PaO_2/FIO_2 ratio, hemoglobin, and platelet count were lower in intubated than non-intubated patients (Xu *et al.*, 2020).

Regarding imaging, the most common findings on initial radiograph were bilateral reticular nodular opacities. Chest computed tomographic scans showed bilateral patchy shadows or ground glass opacity in the lungs of all patients (Arentz *et al.*, 2020a). However, reports noted that at the beginning of the disease course, patients may have normal CXR despite chest involvement as shown by chest CT (Ng *et al.*, 2020a). Thus, chest CT has higher sensitivity than CXR. Song *et al.* reported that ground glass opacities were seen in more than 75% of the patients, along with interstitial and/or interlobular septal thickening (Song *et al.*, 2020). Ng *et al.* introduced ground glass opacities and consolidation in the lung periphery as SARS-CoV-2 imaging hallmarks (Ng *et al.*, 2020a). Consistent findings were demonstrated in other studies (Rodriguez-Morales *et al.*, 2020; Xu *et al.*, 2020; W. Yang *et al.*, 2020; Zhu *et al.*, 2020a, 2020b). A study by Chen *et al.* on 99 patients with SARS-CoV-2 pneumonia in Wuhan, China revealed that 75% of patients had bilateral pneumonia and 14% had multiple mottling and ground glass opacities, based on CXR and chest CT (N. Chen *et al.*, 2020a). Huang *et al.* have shown that 98% of 41 critically ill patients had bilateral involvement based on CT findings. They argued that the typical findings in their study population were bilateral multiple lobular and subsegmental consolidation (Huang *et al.*, 2020).

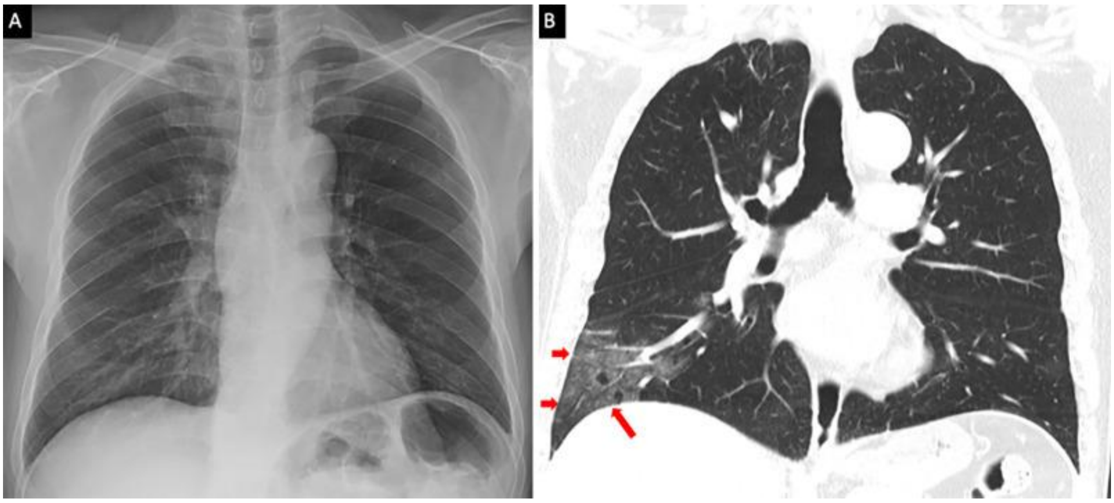

Figure 7: A comparison of, *A,* chest radiograph and, *B,* thorax CT coronal image. The ground-glass opacities in the right lower lobe periphery on the CT (red arrows) are not visible on the chest radiograph, which was taken within 1 hour of the CT.

***Source*:** (Ng *et al.*, 2020a)

2.7.3 Clinical Features, Co-morbidities and Complications

The common clinical features of COVID-19 pneumonia in adults include fever, dry cough, sore throat, headache, fatigue, myalgia and breathlessness (Wang *et al.*, 2020b). The disease manifestations in the infected patients range from mild pneumonia (81%) to moderate pneumonia (hypoxia requiring hospitalization, 14%), and critical illness (leading to invasive mechanical ventilation, multiorgan dysfunction and possibly death, 5%). The risk of death depends on age, underlying comorbidities and severity of the disease, increasing up to 49% in critically ill patients. Underlying comorbidities including cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes and malignancy are associated with increased risk of severity of COVID-19 (Z. Wu & McGoogan, 2020b). The most affected organs were the lungs, followed by the heart, kidneys, liver, brain and gastrointestinal system (Zhou *et al.*, 2020).

A study from five hospitals in Saudi Arabia displayed a high mortality rate of 58.1% in Covid-19 patients admitted to the ICU. Shortness of breath was present in about 85% of the patients (Mutair *et al.*, 2021), which is in concordance with a meta-analysis that proved dyspnea in the COVID-19 patients admitted to the ICU was six times more than in the non-ICU group (Quah *et al.*, 2020b).

Survivors had a higher cough symptom rate compared to the ones that succumbed to death (100% vs 78%; p = 0.015), which suggests that presenting with cough may be more associated with moderate COVID-19 severity or severe COVID-19 with other features associated with a better survival outcome (Quah *et al.*, 2020b). Although a review of multiple studies had illustrated that cough was associated with severe disease (OR 1.63, 95% CI 1.03–2.60), it was not linked with ICU admission (BBC, 2020).

Despite the fact that there have been large advancements in researching sepsis throughout the years, sepsis is as yet one of the main causes of mortality in ICUs. (Jain & Yuan, 2020; Z. Wu & McGoogan, 2020a). Reports from the United States reveal that in nearly 70% of their COVID-19 patients, septic shock was severe enough to necessitate medications to support the heart and circulation (Firth, 1993; C. Wu *et al.*, 2020). Study by Mutair *et al.*, indicated that 84% of patients who died suffered from septic shock ($p < 0.001$) and that septic shock was indicative of expected death in COVID-19 patients admitted in the ICU (OR = 58.1, HR = 9.5) (Mutair *et al.*, 2021). Unfortunately, viral sepsis caused by SARS-CoV-2 has a high rate of being missed and thus daily evaluation of sepsis-related Sequential Organ Failure Assessment (SOFA) score and Multiple Organ Dysfunction (MOD) score is essential for early diagnosis, treatment, and prevention of septic shock and multi-organ dysfunction consequences in COVID-19 patients admitted in the ICU. Similarly, hypogammaglobulinemia that leads to bacterial pneumonia may also be missed during the chaotic situation of COVID-19 (Alsofayan *et al.*, 2020; Kempker & Martin, 2020).

Regarding complications, AKI and ARDS were associated with grave outcomes in critically ill patients ($p < 0.001$) (Mutair *et al.*, 2021). Research has shown that COVID-19 causes exuberant lung inflammation and can result in ARDS and respiratory failure. Although an article had corroborated the advantage of using prednisone in COVID-19 patients utilizing high-dose corticosteroids in critically ill patients is complicated and must be used with extreme care to avoid aggravating complications by worsening laboratory parameters and risk of death (Bhatraju *et al.*, 2020a; D. Liu *et al.*, 2020). Literature reports that the Asian population had the lowest pooled incidence rate of AKI at 5.5% (Alhumaid *et al.*, 2021). Recently, 12 hospitals in New York reported that an estimated 27% of their admitted patients had AKI, however, death among the AKI group was not reported (Kobayashi *et al.*, 2020).

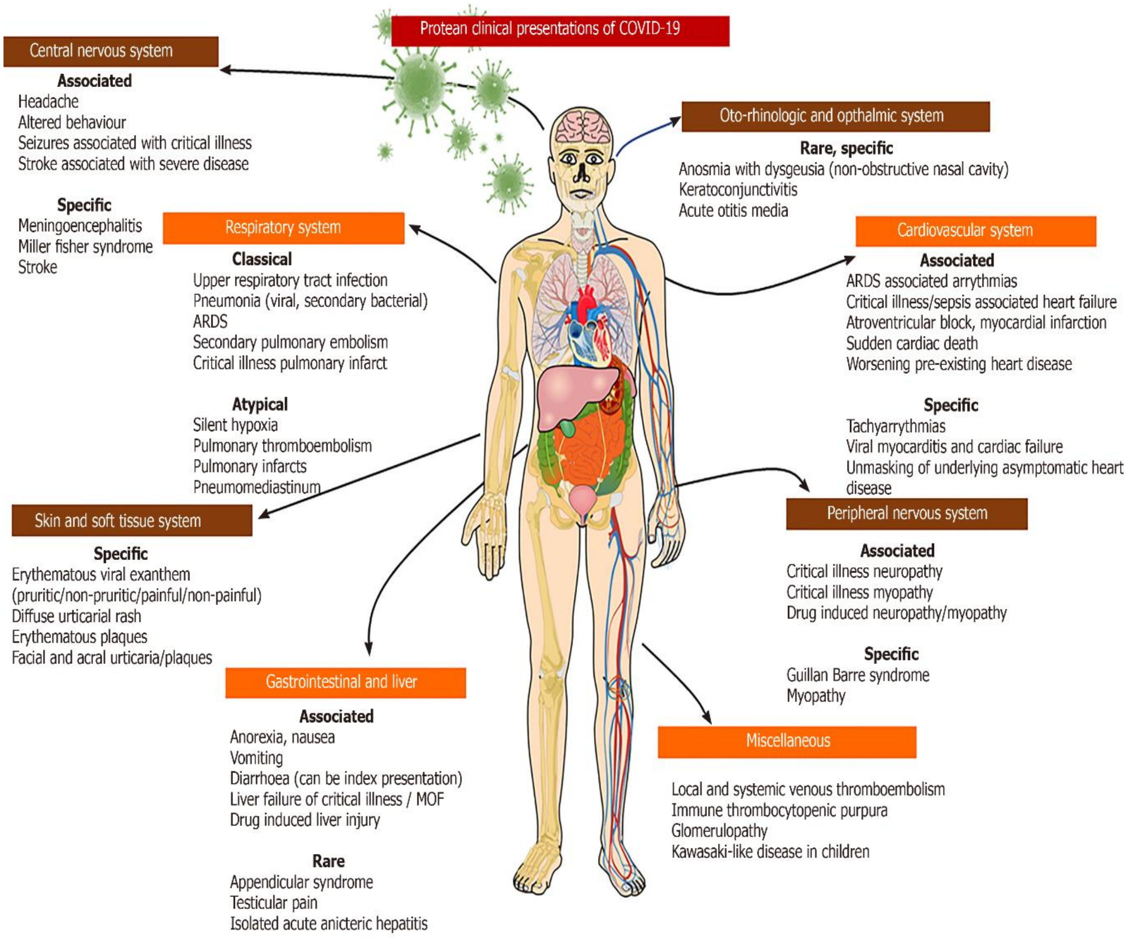

Figure 8: Clinical presentations and organ system involvement of Covid-19

Source: (Vita, 2021)

2.8 Bangladesh Context of ICU-admitted Covid-19 Patients

Bangladesh is estimated to be at high risk for Covid-19 due to its population density, poor sanitary practices, and limited infrastructure and infection control measures. A second wave of Covid- 19 occurred in Bangladesh between April and May 2021, with 90% of cases due to the beta variant of SARS-CoV-2. By August 2021, all cases of Covid-19 in Bangladesh were due to the delta variant, and the death rate was higher than that in the first wave in 2020 (Bari & Sultana, 2021).

In Bangladesh, the Institute of Epidemiology, Disease Control and Research (IEDCR) directed a national level investigation to evaluate the prevalence of Covid-19, in collaboration with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), with support from the US Agency for International Development (USAID) and the Bill and Melinda Gates Foundation. Much epidemiological information about the newly 23 emerging disease remains unknown, including estimates of the proportion of Covid-19 cases in the community, particularly for lower-income regions and countries such as Bangladesh, making it difficult for government policy makers to design optimal containment and mitigation strategies. Prior research has indicated that there may be a considerable number of asymptomatic cases of COVID-19. Other areas requiring further exploration include the incidence rate, prevalence rate, secondary infection rate, incubation period, serial interval and reproductive number of COVID-19 in various settings. It is also important to determine and characterize the immune responses to SARS-CoV-2 infection as well as the clinical and laboratory findings to understand how well the response protects people against future SARS-CoV-2 infection and how long this protection lasts. In this context, laboratory and clinical investigations have the potential to provide precise information about the risk factors and associated co-morbidities, allowing for better management of Covid-19 and to guide public health decision-making.

A 14-day observational Study by Akbar *et al.* (2021) reported that, 62% of the hospital-admitted Covid-19 patients presented cough, followed by fever (~52%). Hypertension (30%) and diabetes mellitus (19%) were two top most associated co-morbidities. The average blood hemoglobin (Hb) level was slightly low among the patients in the early days of infection and went up to the normal level on the later days. A substantial increase in the level of ALT and AST with slightly lower haemoglobin level in COVID-19 patients were observed (Akbar *et al.*, 2021). Hasan *et al.* (2021) reported almost same regarding co-morbidities and symptoms (Hasan *et al.*, 2021). But, those two studies were not ICU-centric, rather generalized with lacking several details.

According to SAHA *et al.* (2021), among 134 ICU-admitted patients 56.5% cases died in intensive care units (ICU) during the study period. The median age was 56 years and 79.2% were male. Clinical outcomes were detrimental due to the comorbidities rather than age and comorbid individuals over 50 were at more risk. Identical biochemical parameters were found in both deceased and surviving cases. Administration of antiviral drug Remdesivir and the glucocorticoid, Dexamethasone increased the proportion of surviving patients slightly (SAHA *et al.*, 2021). Parvin *et al.* (2022) also reported the similar results in case of demographic criteria (Parvin *et al.*, 2022). Still both the studies lack information on vaccination status of the patients, detailed laboratory findings and so on.

Chapter 3- Materials and Methods

3.1 Study Design

Multi-center, retrospective, cross-sectional studies were conducted in this study.

3.2 Study area

This study was conducted in ICUs of 2 government and 4 private specialized hospitals that were authorized for managing most of the critical COVID-19 patients in Chattogram, the prime economic hub and 2nd most populous city of Bangladesh. All the hospitals belonging to the study area were stratified according to their affiliation status; government and private.

3.3 Study period

This study was carried out from 1st April, 2021 to 31st October, 2021.

3.4 Research instruments

A pre-tested semi-structured questionnaire was prepared for the purpose of the study which included all the variables of interest. Demographic features, social history, allergic history and history of co-morbidities were included in the 1st part of the questionnaire while 2nd part recorded the clinical and laboratory findings along with the history of vaccination, management and outcomes of the patients admitted to ICU. The questionnaire is presented in Annex.

3.5 The criteria for ICU admission

Clinical classification and management of all the COVID-19 patients admitted in the hospitals were implemented according to the regulations set nationally for COVID-19 management in Bangladesh (Hayashi, 2020). Based on clinical symptoms, patients were divided into mild, moderate, severe and critical groups.

Patients with uncomplicated upper respiratory tract infection may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise and headache; but no evidence of breathlessness or hypoxia (normal saturation).

Breathlessness and/or hypoxia (saturation 90-93% on room air), respiratory rate of 24 or more and no features of severe disease are considered as moderate.

A patient considered as severe when the patient having a respiratory rate of $\geq$ 30 beats per minute in a resting state and an oxygen saturation of $\leq$ 92% SpO2.

A critical patient should meet any of the following clinical situations:

(a) Respiratory failure occurs and requires mechanical ventilation.

(b) Sepsis or shock occurs.

(c) ICU admission is required for combined organ failure.

In our study, most of the patients were of severe or critical category while only a few met the criteria of moderate group. ARDS was defined according to the Berlin definition (V Marco Ranieri, 2012), septic shock was defined according to the sepsis-3 criteria (Singer *et al.*, 2016) and acute kidney injury (AKI) was defined according to the KDIGO criteria (Khwaja, 2012).

3.6 Case definition: All the patients (moderate to critical group as mentioned above) who were admitted to Covid-19 dedicated ICU with severe acute respiratory illness (fever, cough, sore throat, and breathlessness) irrespective of vaccination status.

Positive test by RT-PCR for testing of COVID19, irrespective of clinical signs and symptoms were considered as confirmed COVID-19 cases.

3.7 Inclusion criteria

1. Confirmed Covid-19 case by positive RT-PCR test.
2. RT-PCR negative but clinically and radiologically suggestive of Covid-19 positive.

3.8 Exclusion criteria

1. Confirmed Covid-19 case but met the criteria for mild group (as mentioned above).
2. Associated confounding infectious diseases such as dengue, malaria, Urinary Tract Infection (UTI) at admission time.
3. Cases with missing variables.

3.9 Study population and data collection

Using 9.16% prevalence of ICU admission for Covid-19 patients in Bangladesh, 95% confidence level and 5% margin of error (SAHA *et al.*, 2021), sample size was determined by following formula-

Sample size, $n = \frac{Z^2\,pq}{d^2}$

Z = 1.96 (Z= Z value of standard normal distribution at 95% Confidence level)

p= Expected prevalence of ICU admission 9.16 % = 0.0916

q = (1 – p)

d = Absolute error or precision 0.05

By placing these values in the formula, $n = 127.86 \approx 128$

Adding design effect of 2, total sample size, 128 X 2 = 256

Considering study duration and availability, 276 ICU patients were enrolled in this study. Simple random sampling technique was followed to fulfill the inclusion criteria.

Therefore, data were collected from 276 COVID-19 patients with definite outcomes who were admitted to Covid-19 designated ICU of Chattogram city. With the approval from concerned department the desired data were extracted from patients' medical records (Case Record Form = CRF) and through direct communication with their attending health care providers.

Epidemiological features including age, sex, contact history, travel history, smoking history, onset of symptoms, vaccination status and its details were noted. Socio-economic status based on monthly income was inscribed too (U. Bangladesh, 2016). Presenting symptoms such as fever, sore throat, cough, nasal discharge, expectoration, fatigue, anorexia, malaise, myalgia, arthralgia, diarrhoea, dyspnoea, nausea, vomiting, chest pain, headache, dysgeusia, anosmia, anorexia, altered sensorium etc. were objectively recorded and included in this study. Co-morbid conditions like diabetes mellitus (DM), hypertension (HTN), cardiac disease, chronic obstructive lung disease or airway diseases including asthma and bronchitis, renal disease, liver disease, malignancy, psychosis, history of stroke, operational procedure like coronary artery bypass grafting (CABG), autoimmune diseases like systemic lupus erythematosus (SLE) and myasthenia gravis were also compiled.

Laboratory parameters including TC-WBC, platelet, Hb (haemoglobin), differential counts of WBC, LDH, ferritin, D-dimer, ALT, AST, serum creatinine, serum electrolytes, IL-6, CRP, PCT (procalcitonin) were noted. Radiological imaging especially chest X-ray and chest HRCT findings were recorded.

Need for HFNC (high flow nasal cannula), NIV (non-invasive ventilation), IMV (invasive mechanical ventilation), antiviral medication (remdesivir), biologics (tocilizumab) were compiled too. Apart from these, we noted any complications such as septic shock, acute kidney injury (AKI), cardiac arrest, heart failure, respiratory failure etc. along with final outcomes.

3.10 Ethical aspect

- Institutional ethical approval was taken from the authorized committee of Chattogram Veterinary and Animal Sciences University (CVASU), Bangladesh.
- Permission for the study was taken from the concerned department from where we collected our desired data.
- Due to the retrospective nature of the study and the anonymity in reviewing patients' data, informed consent from the patients or their legal guardians was waived.
- The interest of the study subjects was not compromised to safeguard their rights and health.

3.11 Statistical analysis

All datasets were entered into Microsoft Excel 21 (Excel 2021, Microsoft Corporation, USA). After cleaning and checking the integrity those were imported into STATA/IC-13 software (Stata Corp. 4905, Lakeway Drive, Texas 77845, USA) for analysis. Descriptive statistical analyses were performed to express categorical variables with numbers and proportions. These were then compared using a chi-square test. *P* values of less than or equal to 0.05 (two-sided) were considered statistically significant.

Chapter 4- Results

In this retrospective study, a total of 276 ICU-admitted COVID-19 patients were included after applying the inclusion criteria and they were stratified into age categories of 22–40 years, 41–54 years, 55–60 years and 60-89 years. Outcomes were presented in this chapter through various tables.

4.1 Socio-demographic status of ICU-admitted Covid-19 patients in Chattogram

Most of the patients were male (58.33%) and came from urban area (83.7%). Although 75.72% of the patients were over 40 years old, the highest proportion (28.62%) was between 41 and 54 years old. About 21.01% of the respondents (n=58) belonged to the 55-60 years age group. The Covid-19 individuals were into diverse professions and interestingly only 52 (18.84%) of them had direct involvement in the healthcare system. Moreover, 57 of the total respondents gave the history of taking Covid-19 vaccine either 1st (6.88%) or both 1st and 2nd doses (13.77%), while almost four-fifths of the (79.35%) patients had no history of vaccination.

Around 74.64% (n=206) of the patients denied any contact with laboratory confirmed Covid-19 cases, although 51.45% (n=142) patients provided the positive family history of Covid-19 infection. Majority of the respondents (45.65%) belonged to the middle class, followed by higher class (40.22%). Nearly all (99.64%; 275/276) patients had infiltrates present on initial chest radiograph. As for medications, 255 (92.39%) patients received antiviral agents, 56 (20.29%) patients received monoclonal antibody. Furthermore, 96 (34.78%) of the total patients with COVID-19 admitted to ICU needed non-invasive mechanical ventilation. None of the patients was treated with extra-corporeal membrane oxygenation (ECMO) and none of them received invasive mechanical ventilation (Table 1).

Table 1: Socio-demographic statistics of the study participants (N=276)

Variable	Category	Frequency	Percent
Gender	Male	161	58.33
	Female	115	41.67
Age (years)	22 to 40	67	24.28
	41 to 54	79	28.62

	55 to 60	58	21.01
	61 to 89	72	26.09
SES	Lower	39	14.13
	Middle	126	45.65
	Higher	111	40.22
Occupation	Non health worker	224	81.16
	Health worker	52	18.84
Area	Rural	45	16.30
	Urban	231	83.70
Smoking habit	Smoker	78	28.26
	Non smoker	198	71.74
Alcoholic	No	273	98.91
	Yes	3	1.09
Vaccination status	No	219	79.35
	1st dose	19	6.88
	2nd dose	38	13.77
In contact with COVID-19 patient within last 14 days	No	206	74.64
	Yes	70	25.36
COVID-19 affected family member	No	134	48.55
	Yes	142	51.45
Clinical status	Mild	0	0
	Moderate	19	6.88
	Severe	112	40.58
	Critical	145	52.54
Mechanical ventilation (NIV)	No	180	65.22
	Yes	96	34.78
Specific antiviral	No	21	7.61
	Yes	255	92.39
Monoclonal antibody	No	220	79.71
	Yes	56	20.29
RT-PCR result	Negative	3	1.09
	Positive	273	98.91
Chest X-ray	Negative	1	0.36
	Positive	275	99.64

4.2 Co-morbidities of the ICU-admitted COVID-19 patients

Diabetes mellitus (145; 52.54%) and hypertension (143; 51.81%) were the most common co-morbidities noted. Other common chronic medical illness included bronchial asthma (23.19%), ischemic heart disease (17.39%), chronic kidney disease (5.8%) and chronic obstructive pulmonary disease (3.62%) (Table 2).

Table 2: Presence of comorbidities among the study subjects

Comorbidities	Present (Frequency)	Present (Percent)
Diabetes	145	52.54
Hypertension	143	51.81
Asthma	64	23.19
IHD	48	17.39
CKD	16	5.80
COPD	10	3.62
CLD	8	2.90
Cancer	3	1.09

4.3 Signs and symptoms of COVID-19 patients admitted to ICU

Table 3 provides a summary of the symptoms present at the time of admission of COVID-19 patients in ICU. Among all symptoms dyspnea (92.75%), fever (90.94%), and cough (78.26%) were the most dominating followed by fatigue (55.8%), myalgia (39.86%) and malaise (38.77%). Other common symptoms were sore throat, nausea, altered smell, chest pain, vomiting, vertigo, diarrhoea, altered taste, runny nose, insomnia, arthralgia and sweating respectively.

Table 3: Frequency of signs and symptoms in COVID-19 patients

Signs/symptoms	Frequency	Percent
Dyspnea	256	92.75
Fever	251	90.94
Cough	216	78.26
Fatigue	154	55.80
Myalgia	110	39.86
Malaise	107	38.77
Sore throat	80	28.99
Nausea	71	25.72
Altered sense of smell	69	25.00
Chest pain	67	24.28
Vomiting	53	19.20
Vertigo	49	17.75
Diarrhea	45	16.30
Altered sense of taste	44	15.94
Runny nose	38	13.77
Insomnia	37	13.41
Arthralgia	27	9.78
Sweating	21	7.61

4.4 Clinico-pathological changes in ICU-admitted COVID-19 patients

We analyzed and summarized the baseline laboratory findings of Covid-19 patients admitted in ICU. As presented in Table 4, it is evident that, almost all the variables showed a significant violation of normality assumption except haemoglobin, platelet count, creatinine and serum electrolytes.

Serum concentrations of CRP, ferritin, PCT and IL-6 were markedly high among the patients, with a maximum value of 282 (mg/L), 5200 (µg/L), 111 (ng/mL) and 5003 (pg/mL) respectively. The mean values were CRP 54.5 ± 58.87 (SD), Ferritin 1073.99 ± 1090.13 (SD), PCT 2.71 ± 12.21(SD), IL-6 239.29 ± 845.81 (SD). Furthermore, the average area of lung involvement in HRCT was 52.41 ± 21.27 (SD), ranging from 0% to 92%.

Leukocytosis, neutrophilia with lymphocytopenia, elevations in D-dimer, LDH, AST and ALT levels were also observed; details in Table 4.

Table 4: Descriptive statistics of clinical pathology of the COVID-19 patients

Tests	Mean	SD	Minimum	Maximum	Normal value
HRCT (%)	52.41	21.27	0	92	-
CRP	54.50	58.87	2	282	<6 mg/L
D-dimer	2.60	3.25	0.1	14.1	<0.5 mg/L
Ferritin	1073.99	1090.13	22	5200	<500 µg/L
LDH	729.23	437.72	55	2711	<248 U/L
Hb	11.81	2.10	5.1	18.2	11.5 – 16.6 g/dL
TC-WBC	16.98	29.11	2.4	261	4 –11 $\times 10^9$/L
Neutrophil	81.05	9.76	57	98	40-75 %
Lymphocyte	15.96	9.17	0.1	36.3	20-45 %
Platelet	249.25	120.88	15	634	150-450 $\times 10^9$/L
ALT (SGPT)	68.40	73.95	3	450	7-55 U/L
AST (SGOT)	69.82	87.65	10	564	8-48 U/L
S. creatinine	1.27	0.89	0.1	8.9	0.5-1.2 mg/dL
Na-ion	138.11	6.16	111	161	136- 145 mmol/L
Chloride-ion	99.29	7.24	9.8	109	95-107 mmol/L
PCT	2.71	12.21	0.01	111	<0.1 ng/mL
IL-6	239.29	845.81	1	5003	<5 pg/mL

4.5 Complications in ICU-admitted Covid-19 patients

Table 5 summarizes the complications of the patients developed during ICU stay. ARDS occurred in 152 (55.07%), cardiac arrest occurred in 66 (23.91%), sepsis occurred in 60 (21.74%) and AKI in 15 (5.43%) of the 276 patients. Respiratory failure, heart failure, myocardial infarction, pulmonary embolism and anxiety were also recorded in some patients.

Table 5: Complications in ICU-admitted Covid-19 patients

Complications	Frequency	Percent
Acute Respiratory Distress Syndrome (ARDS)	152	55.07
Cardiac arrest	66	23.91
Sepsis	60	21.74
Acute kidney injury (AKI)	15	5.43
Respiratory failure	12	4.35
Heart failure	10	3.62
Myocardial infarction	3	1.09
Pulmonary embolism	2	0.72
Anxiety	1	0.36

4.6 Risk factors associated with COVID-19 ICU patients

4.6.1 Univariable analysis to evaluate the potential factors associated with death of COVID-19 patients admitted in ICU (N=276)

It is evident from Table 6 that, increasing age had an increased risk of death, and this was statistically significant. Patients in the age group of >60 years had 3.4 (95% CI) times and 55-60 years had 1.78 ((95% CI) times increased risk of death when compared to 22–40 years of age group. Male gender, non-smoker, patients from middle socio-economic class and rural area were associated with greater odds of poor outcome, although none of those were statistically significant.

Among 276 patients, 103 died (37.3%) and 97 of the deceased had no history of vaccination. Vaccine-naïve patients showed 6.75 (OR 6.7; 95% CI) times increased risk of dying compared to vaccinated ones (either 1 or 2 doses) which was statistically significant too.

Univariate analysis also revealed that, those who were health care providers or had direct involvement in the healthcare system and had a history of contact with COVID-19-positive patient, they experienced better outcome. On the contrary, those who needed mechanical ventilation (OR 4.25; 95% CI), antiviral agents (OR 6.23; 95% CI) or monoclonal antibody (OR 3.8; 95% CI), had an increased risk of poor outcome. All were statistically significant ($p \leq 0.05$).

Table 6: Univariable analysis to evaluate the potential factors associated with death of COVID-19 patients admitted in ICU (N=276)

Factor	**Categories**	**Total number (N)**	***Death (103/276=37.3%)***			
			No. died	**%**	**OR (95% CI)**	***P value***
Gender	Male	161	67	41.61	1.56	0.07
	Female	115	36	31.30	Ref	
Age (years)	22-40=1	67	18	26.87	Ref	0.0009
	41-54=2	79	22	27.85	1.05	
	55-60=3	58	23	39.66	1.78	
	>60=4	72	40	55.56	3.40	
SES	Lower	39	12	30.77	Ref	0.20
	Middle	126	54	42.86	1.68	
	Higher	111	37	33.33	1.12	
Occupation	Non health worker	224	96	42.86	4.82	<0.001
	Health worker	52	7	13.46	Ref	
Area	Rural	45	22	48.89	1.77	0.08
	Urban	231	81	35.06	Ref	
Smoking habit	Smoker	78	72	36.36	Ref	0.60
	Non smoker	198	31	39.74	1.15	
Vaccination status	No	219	97	44.29	6.75	<0.001
	1st dose	19	2	10.53	1	
	2nd dose	38	4	10.53	Ref	
In contact with COVID-19 patient in last 14 days	No	206	88	42.72	2.73	0.001
	Yes	70	15	21.43	Ref	
COVID-19 affected family member	No	134	51	38.06	Ref	0.80
	Yes	142	52	36.62	0.94	
Clinical status	Mild	0	0	0	-	<0.001
	Moderate	19	0	0	-	
	Severe	112	13	11.61	Ref	
	Critical	145	90	62.07	12.46	
Mechanical ventilation	No	180	46	25.56	Ref	<0.001
	Yes	96	57	59.38	4.25	
Specific antiviral	No	21	2	9.52	Ref	0.002
	Yes	255	101	39.61	6.23	
Monoclonal antibody	No	220	69	31.36	Ref	<0.001
	Yes	56	34	60.71	3.38	

4.6.2 Univariable analysis to evaluate the association between presence of comorbidities and death of COVID-19 patients admitted in ICU (N=276)

The table below represents the association between presence of comorbidities and death of ICU-admitted COVID-19 patients. The prevalence of diabetes, CLD and CKD in deceased patients was slightly higher compared to the patients who recovered. Interestingly, patients with asthma survived well and it was statistically significant. On the other hand, none of the patients with cancer was (3/276) survived and greater odd of mortality (OR 3.95; 95% CI) was observed among the patients with ischemic heart disease. Both were significantly associated with poor outcome (Table 7).

Table 7: Univariable analysis to evaluate the association between presence of comorbidities and death of COVID-19 patients admitted in ICU (N=276)

Comorbidities	**Categories**	**Total number (N)**	***Outcome (Death)***			
			No. died	**%**	**OR (95% CI)**	***P value***
Diabetes	Absence	131	43	32.82	Ref	0.14
	Presence	145	60	41.38	1.44	
Hypertension	Absence	133	51	38.35	Ref	0.73
	Presence	143	52	36.36	0.91	
Asthma	Absence	212	86	40.57	Ref.	**0.03**
	Presence	64	17	26.56	0.52	
COPD	Absence	266	10	37.59	Ref	0.62
	Presence	10	3	30.00	0.71	
CLD	Absence	268	100	37.31	Ref	0.99
	Presence	8	3	37.50	1.00	
CKD	Absence	260	94	36.15	Ref	0.11
	Presence	16	9	56.25	2.27	
IHD	Absence	228	72	31.58	Ref	**<0.001**
	Presence	48	31	64.58	3.95	
Cancer	Absence	273	100	36.63	Ref	**0.02***
	Presence	3	3	**100**	-	

*Univariable logistic regression model did not converge. Presenting *P* value of chi square test.

4.6.3 Univariable association between clinicopathological findings with the outcome: death among COVID-19 patients admitted in ICU

The mean values (with ± SE) of laboratory parameters among those who did not survive than those who got discharged were CRP (68.86 ± 6.89 vs 45.90 ± 3.76), ferritin (1472.91 ± 132.19 vs 837.59 ± 68.31), LDH (983.66 ± 39.89 vs 554.42 ± 33.9), AST (93.60 ± 11.51 vs 54.14 ± 5.71), ALT (99.69 ± 9.55 vs 49.48 ± 3.70), serum creatinine (1.41 ± 0.09 vs 1.19 ± 0.06), and these differences were found to be statistically significant. On the contrary, inflammatory markers like D-dimer, PCT and IL-6, all electrolytes except K^+, and all haematological parameters except neutrophil and lymphocyte counts did not show significant differences between survivors and non-survivors. Here, it is evident that, only a slight increase in serum K^+ (5.1 ± 0.39 SE) to the normal level (3.5-5.0 mmol/L) was significantly associated with mortality in ICU admitted COVID-19 patients. More detailed are enlisted in Table 8 below.

Table 8: Univariable association between laboratory findings with the outcome: death among COVID-19 patients admitted in ICU

Variable	Category	Mean	SE	P value
HRCT (% of lung involvement)	Recovered	46.01	1.70	**<0.001**
	Death	63.45	1.61	
CRP	Recovered	45.90	3.76	**0.001**
	Death	68.86	6.89	
D-dimer	Recovered	2.37	0.24	0.12
	Death	3.00	0.32	
Ferritin	Recovered	837.59	68.31	**<0.001**
	Death	1472.91	132.19	
LDH	Recovered	554.42	33.90	**<0.001**
	Death	983.66	39.89	
Hb	Recovered	11.66	0.15	0.12
	Death	12.07	0.20	
TC-WBC	Recovered	18.09	2.74	0.41
	Death	15.12	0.85	
Neutrophil	Recovered	79.23	0.72	**<0.001**
	Death	84.12	0.92	
Lymphocyte	Recovered	17.61	0.70	**0.001**
	Death	13.19	0.82	
Platelet	Recovered	252.51	9.71	0.56
	Death	243.77	10.71	
ALT (SGPT)	Recovered	49.48	3.70	**<0.001**
	Death	99.69	9.55	
AST (SGOT)	Recovered	54.14	5.71	**0.0009**
	Death	93.60	11.51	
Serum creatinine	Recovered	1.19	0.06	**0.05**
	Death	1.41	0.09	
Na^+	Recovered	137.96	0.42	0.60
	Death	138.36	0.69	
K^+	Recovered	4.40	0.06	**0.02**
	Death	5.1	0.39	
Chloride	Recovered	99.32	0.62	0.93
	Death	99.24	0.50	
PCT	Recovered	2.72	1.29	0.98
	Death	2.69	1.21	
IL-6	Recovered	165	76.74	0.16
	Death	341	103.98	

Chapter 5- Discussion

In this study, we utilized the socio-demographic, clinical and laboratory data of 276 critically ill COVID-19 patients admitted in ICU from 6 hospitals in Chattogram to assess the important associations and potential outcomes.

The majority of the cases belong to the age group of 41–54 years followed by 21-40 years age group. This is consistent with the data from a study by Parvin *et al.* (2022) (Parvin *et al.*, 2022). Young people were more affected probably because they were in general unwilling to follow the movement restrictions by the government and maintain necessary preventive practices because they believe that precaution like hand-washing were sufficient enough to go out and ignore social distancing. This data was supported by the other study and showed that younger people are more emotionally negative, self-centered, and less concerned with family (Nelson *et al.*, 2020). Rahim *et al.* (2021) and another retrospective study from Germany also found the similar data (Brehm *et al.*, 2021; Rahim *et al.*, 2020). Again, this is similar to previous research findings where children did not appear susceptible or they could not catch infection easily (Shim *et al.*, 2020). There are many factors protecting children against SARS CoV-2 infection. One of the possible reasons could be due to strong immune response which is secondary to live vaccinations and frequent viral infections. In children, along with good lung regeneration capacity, there is absence of high-risk factors, like ageing related comorbidities and less degree of obesity, smoking as compared to the adult population (Dhochak *et al.*, 2020).

A study by SAHA *et al.* (2020) reported the ICU mortality rate of COVID-19 patients in Bangladesh as 56.5% which is almost 1.5 times of our findings (37.3%) (SAHA *et al.*, 2021). This is obvious, as now-a-days ICU facilities and management in our country are far more promising compared to the year 2020. In addition, different mortality rates in critically ill patients were also reported in different corners of the world, such as 16.7% in China (X. Yang *et al.*, 2020b) to 26% in Lombardy Region, Italy (Grasselli *et al.*, 2020a), 61.5% in Wuhan, China (Wang *et al.*, 2020c), and 67% in Washington State, USA (Arentz *et al.*, 2020b).

The mortality rates get higher if the follow-up time prolongs. Furthermore, a recent study found that critically ill patients had a longer hospital stay with a death rate of up to 60%, resulting in a scarcity of critical care resources (Sang *et al.*, 2021). However, the criteria for ICU admission were different among the studies, which was another reason for the different mortality rates.

In our study, the majority of the deaths (40/72; 55.56%) occurred in the older age group of more than 60 years, which was similar to findings by Priya *et al.* (Priya *et al.*, 2021), in which 59% of deaths occurred in the older age group and various studies (Bhandari *et al.*, 2020; Riverra-Izquierdo *et al.*, 2020; Marimuthu *et al.*, 2021) across the globe. Age-related factors such as declining immune functions, variations in quality and quantity of mucins and glycoproteins on the mucosal barriers and a gradual decline in clearing the inhaled particles could be attributed to increased risk of mortality among the elderly population (Perrotta *et al.*, 2020).

The gender propensity of this study's patients (mostly men) is consistent with that of COVID-19 patients in ICUs in Italy, USA and China (Bhatraju *et al.*, 2020; Grasselli *et al.*, 2020a; Yu *et al.*, 2020). Being the sole bread-earner, males of a family in Bangladesh are more likely to go outside and contract the disease. A study of Mowla *et al.* (2020) conducted in Bangladesh reported similar findings where 63% of patients were men (Mowla *et al.*, 2020). Another study conducted in Bangladesh by Islam *et al.* also observed 65.3% male (Islam *et al.*, 2020).

However, along with the social factors, genetic, hormonal difference, and immunological factors also play important role in the gender disparity. A recent study shows that the difference between the sex could be because of difference in the levels of angiotensin-converting enzyme-2 (ACE2) expression (the first point of contact for SARS- CoV-2 and the human body) in both men and women. ACE2 gene locus is on X-chromosome, which makes women heterozygous and differently assorted as compared to men who are homozygous (Maleki *et al.*, 2020). Along with this, testosterone also play role in the expression of ACE2 which has recently been demonstrated in mice kidneys (J. Liu *et al.*, 2010; Maleki *et al.*, 2020)In general, testosterone plays inhibitory roles in immune processes in contrary to estrogen, which is a possible explanation for men's higher susceptibility to infections (Maleki *et al.*, 2020).

There was a higher proportion of deaths observed in males (41.61%; OR 1.56) when compared to females (31.3%); the study by Li Q (2020) in China reported similar findings (Q. Li *et al.*, 2020). This could be due to the factors such as decreased susceptibility to viral infections and protection attributed to X chromosomes in the female population as noted by Yue *et al.* (2020) and Patrick *et al.* (2022) (Patrick *et al.*, 2022; Yue *et al.*, 2020).

Only 25.36% of our study respondents had contact history with positive COVID-19 patients. It resembles to a study by Priti *et al.* (2020) which has shown that, 84.8% of the patients who tested positive for COVID-19 had neither contact history with COVID-19 positive patients nor had any abroad travel history (Priti *et al.*, 2020). Another study from North India carried out by Mohan *et al.* (2020) in the initial phase of lockdown reported only 4.9% of the patients who had close contact with COVID-19 positive cases (Mohan *et al.*, 2020). However, in a study done in India, 62% of COVID-19 patients had travel history outside India (Gupta *et al.*, 2020). Human-to-human transmission of SARS has occurred in hospital and health care setting, and viral shedding does not occur until symptoms develop (De Wit *et al.*, 2016). But for novel coronavirus, there are some reports that viral shedding occurs days before the onset of disease symptoms (Gandhi *et al.*, 2020; Qian *et al.*, 2020; W. E. Wei *et al.*, 2020). Guan *et al.* (2020) argued that incubation period of SARS-CoV-2 is the same as SARS, and attack rate is up to 83%, by study of a family cluster (Guan *et al.*, 2020b) which supports our finding of COVID-19 affected family history (51.45%).

In our study, most of the patients were from urban area and majority of them from middle socioeconomic class followed by upper class. In our country, the people belong to middle class have to go outside for livelihood, thus infection is very likely. Upper class people typically suffer from various co-morbid conditions due to the lavish lifestyle. Hasan *et al.* (2021) also reported same (Hasan *et al.*, 2021). Regarding the profession, few patients were health care worker (18.84%) which is a bit higher compared to the data from another Bangladeshi study (6%) (SAHA *et al.*, 2021).

In a study done in 7080 fully vaccinated healthcare workers (HCWs) from Christian Medical College, Vellore, the investigators reported the protective effect of vaccination in preventing infection, hospitalization, need for oxygen, and ICU admission as 65%, 77%, 92%, and 94% respectively (Victor *et al.*, 2021). In another study from Chandigarh, the investigators reported the incidence of breakthrough infection as 1.6% (48 of 3000 HCWs); the median time from receipt of the second dose to breakthrough infection was 29.5 days (interquartile range, 20 to 35) (Philomina *et al.*, 2021).

According to Mohan *et al.* (2020), among HCW, only 1.4% reported having contracted the infection while giving clinical care to COVID-19 positive cases (Mohan *et al.*, 2020). This could be due to the vaccination status of the HCWs. Our study shows that, 79.35% of the ICU admitted COVID-19 patients were non-vaccinated and mortality rate was 6.75 times higher compared to the vaccinated patients. Balachandran *et al.* (2022) found the similar results where the study claimed that, ICU admissions (3.5% vs 7.1%) and requirements of non-invasive ventilation (OR 0.5) were less in vaccinated compared to unvaccinated patients. Vaccine naive patients had 4.21 times the risk of death (Balachandran *et al.*, 2022). Furthermore, findings from the study conducted by Verma *et al.* (2021) stated that, those who were vaccinated with COVID vaccine there were 100% recovery rate and zero mortality was found among them (Verma *et al.*, 2021).

The management of patients with several comorbidities is challenging due to their frailty and increased risk of mortality, which is amplified when these comorbid individuals are diagnosed with COVID-19. SAHA *et al.* (2020) found that, older (≥ 50) Bangladeshi male patients with previous comorbidities, such as diabetes, hypertension and heart diseases, are profoundly susceptible to COVID-19. Another finding from this study was that patients with asthma survived well compared to other comorbidities. As with other viruses, SARS-CoV-2 triggers asthma exacerbations, which is why asthma is listed as a risk factor for COVID-19 related morbidity (SAHA *et al.*, 2021). Again, Ejaz *et al.* reported that, there was no significant association of SARS-CoV-2 with asthma (Ejaz *et al.*, 2020). A systematic review of 372 articles describing the underlying diseases of 161,271 patients diagnosed with COVID-19 found that, asthma was reported as a premorbid condition in only 2623 patients accounting for 1.6% of all patients (Mendes *et al.*, 2021). Moreover, it was proposed by Carli *et al.* that, asthma does not seem to be an important premorbid condition in COVID-19 patients; or, conversely, it could be a protective factor (Carli *et al.*, 2021).

These above-mentioned studies immensely support our findings regarding asthma in ICU-admitted COVID patients.

Again, another meta-analysis of 40 studies revealed that coronary heart disease was associated with poor prognosis of COVID-19. After subgroup analysis, coronary heart disease was found to be significantly related to mortality in severe/critical COVID-19 patients (OR = 3.23, 95%CI, $P < 0.001$) (Liang *et al.*, 2021). This is also consistent with our study (OR= 3.95; 95% CI). In addition, our study found significant association between malignancy and high mortality in ICU admitted COVID patients. Kuderer *et al.* reported the same in their study (Kuderer *et al.*, 2020).

In Bangladesh, most people diagnosed with diabetes are from urban areas, and the prevalence of diabetes is highest among those aged from 55 to 59 years (Rahman *et al.*, 2015). Vellingiri *et al.* (2020) observed that high blood pressure, heart disease, lung disease, cancer or diabetes were the commonest comorbidities, while Umakanthan *et al.* (2020) reported cardiovascular disease, lung disease, kidney disease or malignant tumors as the commonest comorbidities (Umakanthan *et al.*, 2020; Vellingiri *et al.*, 2020). Hua Li *et al.* in their study on 138 COVID-19 hospitalized patients reported comorbidities with 31.2% (43) hypertension, 10.1% (14) diabetes, 14.5% (20) cardiovascular disease and 7.2% (10) malignant(H. Li *et al.*, 2020). These findings are different from that of our study wherein diabetes (52.54%) and hypertension (51.81%) were the commonest comorbidities followed by bronchial asthma (23.19%) and ischemic heart disease (17.39%). This is comparable with an Indian study where diabetes mellitus was the commonest comorbidity (50%) followed by hypertension (34.4%), chronic chest conditions (28.1%) and heart disease (12.5%) (Aggarwal *et al.*, 2020). It is consistent with another study from Tehran where most prevalent comorbidities were diabetes mellitus, hypertension and pulmonary disease (Vahedi *et al.*, 2020).

In our study, we reported various symptoms among which, the most common symptom was dyspnea, including 92.75% of the patients at the time of admission, and fever (90.94%) and cough (78.26%) in 2nd and 3rd places. These findings are in accordance with other reports regarding SARS-CoV-2 pneumonia (Chen *et al.*, 2020; Wang *et al.*, 2020, 2020c; Yang *et al.*, 2020). A meta-analysis proved that, dyspnea in the COVID-19 patients admitted to the ICU was six times more than in the non-ICU group (Quah *et al.*, 2020a). All individuals should not necessarily have the triad of fever, dyspnea and cough at the time of admission. Evidence indicated that patients may be afebrile at presentation, and the onset of fever may be delayed (Qian *et al.*, 2020; Rothe *et al.*, 2020). Gastrointestinal involvement has been shown in coronaviruses infections (Leung *et al.*, 2003). The incidence of diarrhea in SARS and MERS infections was reported as 10–30% (Cheng *et al.*, 2004). However, in our study, 45 patients (16.3%) had diarrhea which is also consistent with a study from Tehran (Vahedi *et al.*, 2020).

In our study, 98.91% of the patients had positive RT-PCR for SARS-CoV-2. For whom the PCR results were negative (3/276), diagnosis of SARS-CoV-2 was based mainly on clinical manifestations or imaging findings. Chan *et al.* suggested that lower respiratory tract sample has higher viral load than upper tract in SARS-CoV-2 infections (Chan *et al.*, 2020b). This can be responsible for negative result in infected patients, in addition to the variable sensitivity of detection kits.

Radiologic findings usually include diffuse or multifocal consolidation, pneumonic changes in most of patients suggestive a viral pneumonia (Chan *et al.*, 2020b). Chest CT has higher sensitivity than CXR, as patients may have normal CXR despite chest involvement as shown by chest CT (Ng *et al.*, 2020b). We analyzed the chest HRCT data in our study and the average total lung involvement among all the patients was 52.41±21.27 (SD). This is consistent with another Bangladeshi study done by Parvin *et al.* (2022) where it was 44.83±19.87; indicating a larger involvement than an earlier study by Alam *et al.* (Alam *et al.*, 2020; Parvin *et al.*, 2022).

Several studies have shown increased proinflammatory cytokines in serum of COVID-19 patients; anti-inflammatory agents for COVID-19 therapy highlight the critical role of inflammation in the progression of COVID-19 (Mehta *et al.*, 2020; Stebbing *et al.*, 2020). However, the role of inflammatory markers in monitoring the severity of COVID-19 is still controversial. Recent studies showed that IL-6 and granulocyte-macrophage colony stimulating factor (GM-CSF) could be secreted by the active pathogenic T-cell upon SARS-CoV-2 infection. Also, CD14+ CD16+ inflammatory monocytes activated by GM-CSF could secrete more IL-6 and other inflammatory factors (Y. Zhou *et al.*, 2020). In the study by Chen *et al.*, although no statistically significant difference was found in the level of CRP between the non-severe and the severe group, the mean level of CRP was higher in the severe group than in the non-severe group. Again, the levels of PCT were all higher in the severe group than the non-severe group (L. Chen *et al.*, 2020). According to Zeng *et al.* Patients with COVID-19 in the severe group had higher levels of serum ferritin than those in the non-severe group (Zeng *et al.*, 2020).

In our study, markedly higher levels of C-reactive protein, ferritin, procalcitonin and IL-6 are seen among the study patients while sharp rise in CRP and ferritin showed significant association with mortality. Similar results had been shown by Zeng *et al.* from their meta-analysis of 16 studies and according to them, higher levels of inflammatory markers indicate severity of the disease (Zeng *et al.*, 2020).

The study from Jharkhand claimed that, liver injury is common in COVID-19 patients and alkaline phosphatase is one of the best indicator for Covid-19 induced liver injury (Kumar *et al.*, 2020). LDH is secreted into the extracellular space when the cell membrane is damaged, suggesting viral infection or lung injury, like COVID-19 pneumonia (Mo *et al.*, 2021). Ma *et al.* indicated LDH and CRP as predictive factors for mortality (Ma *et al.*, 2020). These studies explain better why in our study there were significant associations between elevated AST, ALT and LDH with poor outcome.

We observed lymphocytopenia with neutrophilia. The mean WBC count was also high in our study. Vahedi *et al.* reported the same (Vahedi *et al.*, 2020). Liu *et al.* identified the neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for critical illness in patients with COVID-19 infection (Liu *et al.*, 2020). Yang *et al.* reported that more than 80% of the patients in critical setting had lymphocytopenia (Yang *et al.*, 2020).

COVID-19 ultimately leads to death via a variety of complications including septic shock, ARDS, acute kidney injury, cardiac arrest. We found ARDS occurred in 152 (55.07%), cardiac arrest occurred in 66 (23.91%), sepsis occurred in 60 (21.74%) of the 276 patients. Another earlier publication reported that of the COVID-19 patients admitted to the ICU, 61.1% were identified as ARDS, 41.7% received non-invasive ventilation (Wang *et al.*, 2020c). SAHA *et al.* found ARDS in 79.2% and sepsis in 2.4% patients (SAHA *et al.*, 2021).

A cross sectional study from 19 ICUs from Wuhan have found ARDS in 161 (71.2%), septic shock in 34 (15.0%), AKI in 57 (25.2%), and cardiac injury in 61 (27%) of the 226 patients (Yu *et al.*, 2020). These findings are in agreement or similar to the output of our study.

The strength of our study is, we augmented collection of standard clinical and laboratory data from 6 different hospitals with clinically and pathologically relevant biomarkers, concentrations of which were available for nearly all patients.

Although the findings of this study were significant, limitations were also in order. Firstly, laboratory data collection to conduct a broad and extensive study was inevitably challenging as the laboratory results were not systematically collected. Secondly, the evaluated data was extracted retrospectively from patients' medical files and not all laboratory tests were conducted on all patients. A prospective study would give us better insight into the predictors of outcomes in severe COVID-19 patients. Moreover, we did not compare the severe patients with the mild to moderately ill patients. Therefore, more thorough assessment of comorbidities along with clinicopathological parameters in larger samples of critical Bangladeshi patients with COVID-19 are required.

Despite these limitations, this is the largest study on socio-demographic features, clinical-pathological manifestations and disease course among ICU admitted COVID patients from Bangladesh reported to date.

Chapter 6- Conclusion

In light of the exponential growth trend of the increased number of new COVID-19 cases, the critical care resources should be on the top list of the ICU warehouse against the pandemic disease. The clinical and epidemiological characteristics and health outcomes of patients with COVID-19 are significantly different across the patients' age groups and gender. This study highlights the importance of easily recordable basic clinical parameters which can predict the outcomes in COVID 19. Disease severity is associated with rising age, male gender with co-morbidities like IHD, cancer and diabetes. Early identification of elevated inflammatory markers, especially CRP, ferritin and LDH, blood parameters especially lymphocytopenia with neutrophilia, other very important parameters like ALT, AST, creatinine, K^+ would help in providing effective care so that the mortality can be reduced. Considering the main symptoms of ICU admitted COVID patients such as dyspnoea, fever, cough and fatigue can have a key role in providing early warning for the appropriate interventions and thus, in decreasing the mortality rates. It is evident from this study that, vaccines help immensely in minimizing deaths and complications secondary to COVID-19 infection. Therefore, there is a need of awareness and health education about COVID vaccine in community. COVID-19 poses great strains on critical care resources in hospitals and critically ill patients with COVID-19 are associated with considerable rates of severe complications and need treatments of high intensity. We believe that, the findings of this study will help clinicians to decide the appropriate management of COVID-19 patients and take necessary actions to prevent the life-threatening complications.

Chapter 7- Limitations

This study had some limitations as well-

- Data was extracted retrospectively from patients' case record files. A prospective study would give us better insight into the predictors of outcomes in severe COVID-19 patients.
- As some demographic information were collected from the relatives of the patients, there may be a chance of recall bias that can influence the results.
- As data were collected from 6 pre-fixed hospitals, the results of this study may not reflect the exact picture of the whole Chattogram.
- The present study was conducted in short period of time.
- Limited resources and facilities compared to Dhaka.
- The results of pathological investigations vary from one laboratory to other. Thus, it may influence the exact findings.

Chapter 8- Recommendations

Based on the finding of this study, following recommendations are made:

- New cases of COVID-19 continuously appear even under the strict interventions adopted in Bangladesh. Hence, it is recommended that the health care workers including primary care physicians must be oriented in identifying the disease in the early stages through active public health strategies like testing, tracing and treatment on a priority basis.
- Community health campaigns addressing the issues of risk factors for non-communicable diseases would play an important role during this pandemic
- Comparative studies regarding outcomes between vaccinated and unvaccinated COVID patients would be a tremendous approach in settling the fact that, vaccines truly help in reducing death rates and severe complications.
- More researches be carried out to identify various agents, host and environmental factors which may play a significant role in the pathogenesis of severe and fatal infections.
- The policymaker should develop the appropriate provision of sharing up-to date information focusing on all health care workers to expand their perception, knowledge, attitude and practice toward COVID-19 and thus improve their concern level.

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Annex: Questionnaire

Title: Clinico-epidemiological variables affecting outcomes of ICU admitted Covid-19 patients in Chattogram.

SL No:

Case record form

Date:

Name: **Age:** Yrs. **Sex**: M / F / T

Religion: **Ethnicity:** Bengali /Tribal /Others **Phone no**:

Address: Division……… District……………. Thana…………… Union…………
Ward no- ……. Road no- ………. House no- ……… **Area-** Rural/Urban/ Slum

Socio-economic status:

Lower (<Tk 10,657) / Middle (Tk 10,657 – 25,763) / Upper (>Tk 25763)

Marital status: Single/ Married/ Divorced/ Widowed **Blood group:**

Occupation: Health workers**-** Doctor/Nurse/Med. technologist/Ward boy/MLSS/…

Non-health workers**-**Housewife/Farmer/laborer/Driver/Police/Teacher/Banker/others.

Smoking history: Y/N **Alcohol-** Regular/Occasional /No **Allergy:** Y/N

Comorbidity: None(0)/DM(1)/HTN(2)/Asthma(3)/COPD(4)/CLD(5)/CKD(6)/IHD(7) /Obesity(8)/Cancer(9)//HIV(10)/TB(11)/Others(12)

PART 2

1.Date of onset of symptoms- **DOHA** (if)-

2. Patient get infected: Once/ Twice/ More **Season -** summer /winter /spring

3. Contact with Covid19 patient in last 14 days**:** Yes /No

4. Within last 14 days, visited: Mosque (1) / Temple (2) / Market (3) / Public transport (4) / Social gathering (5) / Tourist spot (6) / others (7) ……

5. Vaccination history: Yes/ No **if yes-** 1st dose/ both 1st & 2nd dose

If yes, how many days after vaccination did the patient get infected? ……days

Medical emergency immediately after taking the dose: None / Anaphylaxis/ others

severe symptoms/complications after vaccination: Yes/ No (if yes, after ……days)

If yes, specify the complication/s………………

6. Transmission: *Family members get infected* – **Y/N**

Symptoms occurred first in- the patient /Family members

Infected			**Not infected**		
Age	**Sex**	**Vaccination status**	**Age**	**Sex**	**Vaccination status**
	M / F	Yes / No		M / F	Yes / No
	M / F	Yes / No		M / F	Yes / No
	M / F	Yes / No		M / F	Yes / No

Symptoms: Fever (1)/ Cough (2)/ Dyspnoea (3)/ altered sense of smell (4)/ altered sense of taste (5)/ fatigue (6)/ sore-throat (7)/ diarrhoea (8)/ nausea (9)/ vomiting (10)/ anorexia (11)/ headache (12)/ confusion (13)/ congestion (14)/ conjunctivitis (15)/ chest pain (16)/ myalgia (17)/ malaise (18)/ covid tongue (19)/ insomnia (20)/ others (21)

7. Clinical status: Asymptomatic/Mild/Moderate/Severe/Critical

8. Lab & imaging:

Test	**Result**	**Test**	**Result**
RT-PCR	Positive / Negative	**CRP**	
Chest X-ray		**D- dimer**	
CT/HRCT	…………%	**Ferritin**	
PCT		**LDH**	

Hb%.............. **TC-WBC:** …… **Neu:** ……. % **Lymph:** ……% **Platelet:** ………

IL-6: ……. **ALT:** ………. **AST:** ……… **HbA1C:** **S. Creatinine:**

S. electrolytes- Na^+ …………. K^+ ……………… Cl^- ……………. HCO_3^- ………

9. SpO_2: … % **GCS:** ……/15 **Mechanical Ventilation (NIV):** Yes/No

10. Specific antiviral: Yes/No **Specific biologics**: Yes/ No

11. Severe complication: ARDS/Cardiac arrest/Stroke/Post covid diabetes / psychosis/ Encephalitis/Meningitis/Heart failure/AKI/ PE/ …….

12.Outcome: Recovered/ Death.