TITLE: Sex and gender variations in patients with an infectious disease of COVID-19 epidemiology in Bangladesh: A comprehensive review

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ABSTRACT:

The novel coronavirus disease has been analyzed as the cause of an outbreak of severe acute respiratory syndrome (SARS-CoV-2) infection with over 312,996 total cases and over 3,983 deaths in Bangladesh as of August 31, 2020. COVID-19 infection showed that a variation number of cases and deaths between the sex differences in immune responses to viruses and gender related risk factors among the male and female, but more severe outcomes in aged men of cases and deaths in 31- 40 and 61-70 years respectively than female. However, the epidemiology of SARS-CoV packages their nucleocapsid phosphoprotein (N proteins) may cross-react with COVID-19 in the viral genome into a helical ribonucleocapsid and plays a central role to viral self-assembly and suppressing the RNA interference (RNAi) to overcome the host defense. Hence, most of the Covid-19 infected patients diagnosed and specified with RT-PCR, CT scan, LAMP, NGS, serological tests have become the assessment of the disease. Our mini-review focuses on Sex and gender variations with COVID-19 and their effective management, diagnosis, treatment, and prevention of patients in Bangladesh.

Keywords: COVID-19, SARS-CoV-2, Sex, Gender, RNAi, ACE2, TMPRSS2

INTRODUCTION

In Wuhan, the capital of China's Hubei-Province; a new coronavirus, SARS-Cov-2 which means severe acute respiratory syndrome coronavirus two became probably regarded as a consequence of a series of infections in the lower respiratory-tract, just at the close of 2019. WHO has formally termed the latest SARS-CoV2 viral disease 'COVID-19' on the 11th of February 2020 [1]. Since the officially confirmed pathogenic factors release was released on the 7th of January 2020 and their genome sequence was posted upon that internet web resource virological.org²; three days later, their four genomes sequence database published by GISAID (which offers unrestricted entry to influenza-virus genomic information) on 12 February 2012. The genome sequences recommend the viral intimately allied with SARS-CoV. Coronaviruses have the single-stranded RNA genome in the positive(+ve) sense, infecting humans as well as a wide variety of species [2]. Four forms of coronavirus (a, b, g, d) have already existed. There are two types of human coronavirus(HCoV): coronavirus A (Human coronavirus-229E and NL63) and coronavirus-B(MERS-Corona virus, SARS-Coronavirus, Human coronavirus-OC43, and Human coronavirus-HKU1) [3]. An initial devastating problem was reported on the 11th of January 2020. The Pandemic was sparked up mostly during the Chinese New Year in case of the huge Chinese transition. In a few other Chinese provinces, also other country's issues were also recorded in people who mostly returned from Wuhan [4]. The overall amount of verified cases was three hundred and forty were published on January 22, 2020, and six patients were declared dead. The existence of a novel coronavirus 2019 human infection from China was confirmed by Thailand, Japan, and Korea on January 13th, 16th, and 21st respectively. Currently, nCoV-19 expanded everywhere throughout the globe to an area including counties of two hundred. Statistics and reports, as of the 14th of August 2020, the number of recorded incidents in china reached 84,786; 4634 were dead, and 79,462 were recovered. Although Covid19 was originally from China; however, in Brazil and the USA upwards of 100,000 people died. Coronaviruses have risen repeatedly in various places around the globe throughout the last several years. SARS coronavirus syndrome (SARS-CoV) occurred, in the initial period of the twenty-first-century; infecting approximately 8,422 people worldwide throughout the pandemic and causing 916 deaths. Middle East Coronavirus Respiratory Syndrome (MERS-CoV) become acknowledged for the first-time science 2012, introducing the highest of 1,401 were infected of this virus and 543 (approximately 39percent) where it died (World Health Organization, MERS-CoV). As per the world meter, by 14th August of 2020, the maximum pandemic spread across 215 countries and territories and reported deaths were 760,342 throughout the previous month in which a total of 173,512 people died. (<https://www.worldometers.info/coronavirus>). Most flu-like symptoms of SARS-CoV-2 are similar to other coronaviruses, such as fever, cough, and asthenia [5]. COVID-19 Disease may occur seem to be mild to severe pneumonia or as an asymptomatic infection [6]. Becoming an enduring challenge towards diagnostics channels has become a mixture of high transmission speeds, high incidents, and vast numbers of asymptomatic including with "pre-symptomatic" transmission[7]. Even though RT-PCR continues to remain the benchmark with a reliable test of COVID-19, high false-negative rates and lack of exposure to an early-stage RT-PCR assay impair the assessment of the patients affected in an early period. Frequent CoV occurrences

and crises point to a threat to public health. This suggests that new emerging CVs can be transmitted from animals to humans and humans to humans [8].

CLASSIFICATION OF SARS-COV-2

SARS-CoV-2 is a recently discovered human coronavirus that attacks the respiratory system and causes CoVid-19 disease. The International Committee on Taxonomy of Viruses (ICTV) classified coronaviruses under the order Nidovirales, family Coronaviridae, and subfamily Coronavirina [9]. Different genomic and serological evidence shows that the subfamily Coronavirinae is further classified into the next four genera (figure 1); *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*, of which *alpha* and *betacoronavirus* only have known infectious for human. The next-generation genomic sequence and phylogenetic analysis reveal a subgenus of the *Betacoronavirus* genus named Sarbecovirus [10]. SARS-CoV-2 belongs to the sarbecovirus sub genus of *betacoronavirus* genus [11]. Besides SARS-CoV-2, another six discovered HCoV known as HCoV-NL63 and HCoV-229E belongs to *Alphacoronavirus*; while on the other hand, HCoV-HKU1, HCoV-OC43, SARS-CoV, and MERS-CoV belong to *Betacoronavirus* [12]. SARS-CoV and MERS-CoV are the most pathogenic for human and they are responsible for the two worldwide outbreaks; SARS in 2002-3 with 8,437 lab reports and 813 case fatality and MARS in 2012 with 2,494 cases and 858 death. SARS-COV-2 is the seventh human coronavirus [13] with 14,535,008 lab identified cases and 606,810 case fatality and the number is increasing by the time [14].

GENOMIC STRUCTURE OF SARS-COV-2

The SARS-CoV-2 comprises a non-segmented genome with 29.9 kb long single standard positive-sense RNA (+ssRNA) [9, 15]. The genome contains a 5' untranslated region (UTR) and a 3' untranslated poly (A) tail region which allows it to function as an mRNA for the translation of replicase polyprotein (figure 2). The genome is split into two main regions: structural and non-structural parts. The genetic makeup of the non-structural parts is composed of two open reading fragments (ORF) named ORF1a and ORF1ab which are responsible for encoding the non-structural protein (nsps). Several types of replication-transcription complex encoded by these nsps. ORF1a occupies most of the genome and encodes a total of eleven non-structural proteins (NSP1-NSP11) while ORF1b encodes 5 nsps (NSP12-NSP16). These 16 nsps are encoded by two polyprotein pp1a and pp1ab to form a replication-transcription complex (RTC) in double membrane vesicles (DMVs). Two proteases called 3C like serine protease (3CLpro) and papain like cysteine protease (PLpro) functions to cleave these polyproteins. Including these, RNA dependent RNA polymerase (RdRp) and helicase (Hel) are also important for transcription and replication of CoVs found in the ORF1b region in the genome of SARS-CoV-2 virus [16].

The most important 4 structural proteins of the SARS-CoV-2 encoded by the 3' end region of the genome. These proteins are (spike glycoprotein (S)), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N)). SARS-CoV-2 depends on their spike protein for binding to the host cell surface receptor through the receptor-binding domain (RBD) [17].

The closely related other human coronaviruses to the SARS-CoV-2 is MERS-CoV and SARS-CoV. The length of each virus is approximately 30,119 nucleotides long. The genetic makeup of both viruses contains a 5' cap and a 3' poly (A) tail end. The rep gene of each virus contains 16 NSPs numbered as nsps1-nsps16 as like as SARS-CoV-2. At around the end of the 3' tail, the gene comprises 4 structural genes; S, E, M, and N. Besides these genes, MERS contains more 5 accessory proteins (ORF3, ORF4a, ORF4b, ORF5, ORF8) and SARS contains 8 accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8a, ORF8b, ORF9b) whereas SARS-CoV-2 contains 9 more accessory proteins (ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, ORF10). The SARS-CoV-2 is relatively more infectious in comparison to the other HCoV like MERS-CoV and SARS-CoV. It's possible for the epidemiological dynamic characteristics of the virus [18].

LIFE CYCLE OF SARS-COV-2

The life cycle of SARS-CoV2 Viral entry tends to consist of both a balanced viri. The life cycle of SARS-CoV2 Viral entry tends to consist of both a balanced virion and the host-cell interaction. The viral particle interacts mostly on the surface of the cell with certain proteins and triggers infection [19]. SARS-Coronavirus-2 penetrated the cells via a virus surface protein called a spike. SARS-Coronavirus-2 interact with its human ACE2 receptor (hACE2) through its receptor-binding domain (RBD) for performing its function (figure 3) [20]. The spikes protein conformational modification occurs after reception binding facilitates the combination of viral envelopes through the endosomal pathway with the membrane of the cell [21]. Then release into the viral genome cytoplasm. In all coronaviruses, the genomes are identical in structure. Each replicase gene of roughly 20 to 22 kb passes to 5 primes. Gene containing Replicase which products are encrypted into two significant fragments, open-read fragments 1a and 1b, which are converted into pp1a as well as pp1ab and then divided into small products through viral proteinase. Finally, virus particles and genetic material of RNA were packaged in the endoplasmic reticulum and Golgi and then transported through vesicles to escape on and host-cell interaction [22]. The viral particle interacts mostly on the surface of the cell with certain proteins and triggers infection [19]. SARS-Coronavirus-2 penetrated the cells via a virus surface protein called a spike. SARS-Coronavirus-2 interact with its human ACE2 receptor (hACE2) through its receptor-binding domain (RBD) for performing its function (figure 3) [20]. The spikes protein conformational modification occurs after reception binding facilitates the combination of viral envelopes through the endosomal pathway with the membrane of the cell [21]. Then release into the viral genome cytoplasm. In all coronaviruses, the genomes are identical in structure. Each replicase gene of roughly 20 to 22 kb passes to 5 primes. Gene containing Replicase which products are encrypted into two significant fragments, open-read fragments 1a and 1b, which are converted into pp1a as well

as pp1ab and then divided into small products through viral proteinase. Finally, virus particles and genetic material of RNA were packaged in the endoplasmic reticulum and Golgi and then transported through vesicles to escape [22].

SEX DIFFERENCES IN COVID-19 EPIDEMIOLOGY AND CASE FATALITY IN BANGLADESH

As of 31 August 2020 confirmed cases for male (figure 4), 1.8% cases were confirmed in male between 01 and 10 years old, 2.8% in the age group of 11 to 20, 13.9% in the age group of 21 to 30, 20.4% in the age group of 31 to 40, 1.9% in the age group of 41 to 50, 11.1% in the age group of 51 to 60, 5.3% in 61 to 70 years old, 2.0% in 71 to 80 years and 0.6% in the age group above 80 years old male. On the other hand the female case reported that (figure 4) 1.2% cases were confirmed in female between 01 and 10 years old, 2.4% in the age group of 11 to 20, 6.6% in the age group of 21 to 30, 6.5% in the age group of 31 to 40, 4.9% in the age group of 41 to 50, 3.9% in the age group of 51 to 60, 2.0% 61 to 70 years old, 0.6% in 71 to 80 years and 0.2% in the age group above 80 years old female. The highest case rate for male 20.4% was reported in the age group of 31 to 40 years old, but in female highest case rate 6.6% was reported in the age group of 21 to 30 years old. Male and female represented 72% and 28% of the total reported confirmed COVID-19 cases respectively.

For male death reported that (figure 5) the highest death rate 24.6% was reported in the age group of 61 to 70 years old, 0.1% in the age group of 01 and 10 years old, 0.4% in the age group of 11 to 20, 1.0% in the age group of 21 to 30, 3.8% in the age group of 31 to 40, 7.8% in the age group of 41 to 50, 18.9% in the age group of 51 to 60, 16.4% in 71 to 80 years and 5.5% in the age group above 80 years old male. For female death reported that (figure 5) the highest death rate 6.6% was reported in the age group of 61 to 70 years old, 0.2% in the age group of 01 and 10 years old, 0.3% in the age group of 11 to 20, 0.9% in the age group of 21 to 30, 1.5% in the age group of 31 to 40, 2.3% in the age group of 41 to 50, 4.6% in the age group of 51 to 60, 3.3% in 71 to 80 years and 1.7% in the age group above 80 years old male.

Male and female represented 78% and 22% of the total reported confirmed COVID-19 deaths respectively [23-29]. 31 August 2020 in Bangladesh, the total test, confirm case, active case, hospitalization, ICU cases, recovery and deaths are shown in figure 6.

SEX DIFFERENCES IN ACE2 AND TMPRSS2 REGULATION

As figure 7 showed that SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) enzyme as receptor to bind with a cell. ACE2 is an outer membrane protein which is found in different types of cells; adipose tissue, heart, spleen, blood vessels, kidneys, liver, lungs, and bladder [30, 31]. The S protein of SARS-CoV-2 binds to the ACE2 receptor of the cell and invade the target cell. Some recent studies have shown that the levels of circulating ACE2 is higher in women compared than man in healthy and diabetic states. Some other studies found higher ACE2 serum activity in the old age female compared to younger [32].

The second important protein for SARS-CoV-2 to invade a cell is transmembrane protease serine 2 (TMPRSS2), expressed in the cell epithelium and most of the human prostate cancer metastases predominantly. TMPRSS 2 actually helps SARS-CoV-2 to priming with target cell. The concentration of testosterone hormone in the cell helps to activate androgen receptor (ARs) via heat shock proteins (HSPs). These ARs are then phosphorylated and translocated into the nucleus and speed up the translation process of TMPRSS 2 protein in the cell. Finally, these large number of TMPRSS 2 spreads at the outer membrane of the cell and activate the spike proteins of SARS-CoV-2 [33].

SEX DIFFERENCES IN IMMUNE RESPONSES TO VIRUSES

The vulnerability of both women and men to viral infections differs and tends to sexual disparities in the severity and seriousness of disease[34]. Gender and sex may have a wide variety of impacts on the unequal vulnerability of men and women in infectious diseases induced by viruses. Humans, for example, found that women are more than 40 percent lower in proliferation than men with human immunodeficiency virus (HIV). Although there is a less transmitting HIV RNA than men, the chances of getting AIDS is 1.6 times higher for women who've been compared to men on their HIV RNA loads [35]. Even if the sensitivity to influenza A is frequently greater in men, fatalities are noticed to be higher in women's results of exposure to pathogenic influenza A viruses [36]. By contrast, the prevalence of surface antigen serum hepatitis B virus (HBV), titers of HBV-DNA, and hepatocellular carcinoma development are higher amongst men than women [37].

Innate viral recognition and responses and downstream adaptive immune responses vary among women and men throughout viral infections. Innate immune cells, particularly monocytes, macrophages, and dendritic cells (DCs), and inflammatory immune responses, typically have more numbers and involvement in women relative to men[38]. Toll-like receptor (TLR)7, used to detect single-stranded RNA viruses, including coronaviruses. The TLR7 gene can evade the suppression of the X chromosome and increase the level of TLR7 in women in comparison to men [39]. In vitro exposure of TLR7 ligands to peripheral-blood mononuclear cells (PBMCs) leads to increased interferon- α (IFN α) synthesis from woman cells, as compared to man cells [40].

As regards to adaptive immune responses, the humor and cell-mediated immune response of women, in general, is higher than that of men for antigenic stimulation, vaccination, and infection [41]. Almost all basal immunoglobulin levels are significantly higher in women than men and also antibody response levels[42]. Worldwide analyzes of B-cell signatures show that the most expression levels genes in B cells in adult women are substantially more regulated than in men [43]. Research studies have shown that mans had lower CD3 +, CD4+: CD8 +, and T type 1 (Th1) cell aids than women [44]. The sexual differences in immune responses can also be caused by polymorphisms of sexual chromosomes along with autosomal genes that express immune proteins [45]. Sexual differences in cardiac tissue

immune response often rely on age. Since then, it has been shown that women build strong chronic immune reactions in old age with myocardium [46].

GENDER-RELATED RISK FACTORS AND IMPACT

During this pandemic situation of COVID-19, fatality rates in severe cases are less in women than men. Men are more susceptible to coronavirus than women. Though the actual specific reason is not clear yet, some gender-related risk factors are vastly responsible for these differences (figure 8) [47]. The human sex chromosomes X and Y differentiate between men and women. Where women have two copies of the X chromosome while men have only one copy of the X chromosome and one copy of the Y chromosome[48]. Women have less inflammation and lower level of viral load than men because some genes are encoded by the X chromosome are linked to immune responses. Immune cells of women can be activated more compared to men, and these are related to the INF (Interferon) production and stimulation of TLR-7 (toll-like receptor-7). Higher T cell activation in women creates a rapid immune response against coronavirus compared to men[49]. The X chromosome is more functional in women which are highly dense with immune-associated cells, this makes women greatly stronger in rapid immune responses (innate and adaptive) compared to men [50]. Also, sex hormones make women stronger than men in case of viral infection. Estrogen increases immune responses as well as rapid pathogen decline and effective vaccination while inhibitory roles are played by testosterone for immune responses. It may a valid reason for men's higher fatality rate[40]. Hypertension, chronic lung disease, cardiovascular disease, such comorbidities are possible fatal risk factors for severe COVID-19 patients[51]. Lifestyle, behaviors like drinking, and smoking are higher in men than women. This lifestyle plays a vital role in developing such comorbidities. These comorbidities rate is higher in men than women worldwide. This also makes men more vulnerable to COVID-19 than women [52, 53].

TRANSMISSION

The transmission of SARS-CoV-2 most likely happened between very similar contacts like household-sharing individuals (figure 9). The period that cases are infectious in the population is minimized by isolation and touch monitoring. Nevertheless, the number of asymptomatic cases is unknown and highly dependent. The risk of infection for children in the general population is high[54].SARS-CoV-2 general secondary assault rate was 16.3 percent above the rates of two other respiratory diseases associated with coronavirus, SARS, and MERS [55]and is 13 percent higher than influenza a pandemic of 2009. The asymptomatic carrier may have transmitted coronavirus. A further study is required to determine the process by which asymptomatic transports may acquire and transmit the COVID-19 coronavirus [55]. Generally, vertical transmission after primary maternal infection takes place through trans-placenta, ingest, or aspire to cervicovaginal secretions, and postpartum via breastfeeding during intrauterine life[56].COVID-19 In new mothers, pneumonia had clinical signs similar to those of non-pregnant elderly patients with COVID-

19 pneumonia. There is also no evidence of intrauterine infections among women to perceive late pregnancy COVID-19 pneumonia triggered by vertical transmission [57]. In a study from China in 2020, it was shown that the ventilation systems of COVID-19 patients in hospital rooms contain virus particles from the SARS-CoV-2 [58]. Although the biophysical production of droplets and gas cloud formation for patients infected by the SARS-CoV-2 virus has not been specifically assessed, this pathogen may have many characteristics of the exhaled gas cloud and respiratory transmission [59]. High temperatures and high moisture will decrease influenza transmission. First, in cold climates, the influenza virus becomes more stable and breathing particles stay airborne in warm air for longer to reservoirs of viruses. Second, relatively cool and drier weather can also decrease host defenses system and increase their vulnerability to the virus. Findings also illustrate the evidence that high temperatures and high relative humidity minimize SARS coronavirus viability [60].

DIAGNOSIS METHODS FOR COVID-19

It's because no verified vaccines or drugs have not yet been discovered against COVID-19; appropriate diagnostic approaches can reduce the present pandemic situation [60]. Though various diagnostic methods are present for the identification of the virus and fighting against the current pandemic situation, these methods also possess some drawbacks [61]. These diagnostic methods are based on two types according to their speed and accuracy of result generation time, and handy [62].

Nucleic acid-based method

DNA/RNA as genetic materials are used in Nucleic acid-based methods, which are relatively rapid than the conventional methods. These diagnostic approaches are applicable for high-throughput research but are comparatively expensive. Many emerging diagnostic technologies based on their nucleic acid are NGS (Next-generation sequencing), RT-PCR, LAMP (Loop-mediated isothermal amplification) [60].

Next-generation sequencing (NGS)

This method is also known as HTS (high-throughput sequencing) and identifies genomic sequences (in a single experiment, more than 1 million base pairs). By NGS method, findings of novel viral strain on a large scale are not only possible but also quick identification of these strains which are responsible for human diseases are possible [61]. But the enormous cost of the chemicals and apparatus needs for NGS limits its use in laboratories for disease diagnosis. While NGS is costly and requires sophisticated equipment, RT-qPCR is a better choice in terms of availability and regular testing [60].

RT-PCR

The most effective diagnostic technique is molecular testing using Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) because of its ability to track or recognize particular pathogens [61]. For the identification of viruses from airway secretions, this approach is widely used in case of acute respiratory infections. The test sample is obtained by mopping the nasopharyngeal with a cotton bud, or spitting is used to extract the sputum. Then viral transport media is applied[60]. RNA is derived from the samples using extraction kits, which is converted through the reverse transcription process to complementary DNA (cDNA), followed by specific region amplification via primers [62]. The primers and samples which target different SARS-CoV-2 genes are used as diagnostic tests in real-time RT-PCR assays. The envelope (E), RNA-dependent polymerase gene (RdRp), first open reading frames (ORF 1a and 1b), and nucleocapsid (N) are the primary diagnostic targets for identification of COVID-19 [63]. Then the PCR test takes place after optimizing the conditions of the assay by taking stringent measures to set reagent state, incubation times, and temperatures. Controls must be carefully selected to ensure test reliability and to identify experimental failures[62]. However, this technique has disadvantages as it takes longer to yield results, a higher possibility of false-positive results, may occur infection from collected samples, and sometimes clumsy mixing solutions procedures [60].

Loop-mediated isothermal amplification (LAMP)

Loop-mediated isothermal amplification (LAMP) is a novel type of amplification of the isothermal nucleic acid [64]. The technique is based on target DNA synthesis, using specially formulated primers and enzyme (DNA polymerase) at a constant temperature of 60–65°C [61]. Initially, LAMP recognizes the target by six distinct sequences and, later, by four distinct sequences, the target sequence is supposed to be amplified with high selectivity[65]. LAMP reduces the time and cost of detecting coronavirus as though it is a relatively faster assay, and costly equipment and reagents are not necessary [64].

Serological Tests

Various serological assays are being used widely right now [62]. Classify the specific antibody complex produced in a virus-infected individual is the result of its immune response against that virus; it is the key concept of serological tests. ELISA (Enzyme-Linked Immunosorbent Assay), RDT (Rapid Diagnostic Test), and Assay for Neutralization are some serological tests [60]. RDT is the fastest immunoassay than Assay of Neutralization and ELISA test. For result generation, Assay of Neutralization takes 3-5 days, and ELISA takes 1-5 h, where RDT takes 10-30 minutes only [39, 62]. ELISA kit's sensitivity to SARS-CoV-2 is still under investigation. The test kit has also shown some false-negative results [61, 62].

Computed Tomography (CT) Scan

Computed Tomography Scan is a high-sensitive diagnostic approach. Before appearing clinical symptoms, results can be shown by this technique; hence many researchers suggest this [61]. The computed tomographic imaging anomalies characteristic of the chest for

COVID-19 are diffuse, peripheral ground-glass opacities. The results of chest computed tomographic imaging are non-specific and overlap with other infections, so the diagnostic value for COVID-19 of chest computed tomographic imaging is minimal [66].

TREATMENT OF COVID-19

Though verified vaccine and specific antiviral treatment are not available right now, isolation remains the most effective method for COVID-19 containment. According to the clinical severity of confirmed coronavirus disease, patients require the following managements [67-69], supportive therapies are appropriate for moderate symptoms containing patients at an early stage [70]. The use of acetaminophen, oxygen therapy, external cooling, antibacterial treatment, and dietary supplements will accomplish this[68]. Administration of convalescent plasma, high flow oxygen therapy, glucocorticoid therapy are applied for severely ill patients [70]. Moreover to these therapies, the following classes of drugs for successful treatment of COVID-19 are evaluated: antivirals (e.g., remdesivir, favipiravir), anti-inflammatory agents (dexamethasone, statins), antibodies (e.g., convalescent plasma, hyperimmune immunoglobulins), targeted immunomodulatory therapies (e.g., tocilizumab, sarilumab, anakinra, ruxolitinib), antifibrotics (e.g., tyrosine kinase inhibitors) and anticoagulants (e.g., heparin) [66].Some possible promising therapeutic options for COVID-19 treatment are presented in the figure 10 [71].

SOME POSSIBLE DRUGS AGAINST COVID-19

Some drugs like hydroxychloroquine, remdesivir, favipiravir, lopinavir–ritonavir conjugated therapy have been shown promising result in some trial cases. Their trial reports are extracted in table 1.

Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine have been used to treat malaria and amoebiasis [72]. In in vitro and in vivo trials, chloroquine and hydroxychloroquine were showing antiviral activity against SARS-CoV-2. Hydroxychloroquine was found to have greater antiviral activity than chloroquine [71]. Chloroquine and hydroxychloroquine may inhibit coronavirus through a series of steps such as inhibiting viral integration to the plasma membrane, changing the pH of the plasma membrane surface, and may also inhibit nucleic acid reproduction [73]. Results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in improving lung imaging findings, inhibiting the exacerbation of pneumonia, shortening the disease course and promoting a virus negative conversion [74].

Remdesivir

In China, remdesivir is widely used for COVID-19 patients[75]. It is metabolized into its native form, which interferes with viral RNA production resulting in a decrease in the

development of viral RNA. Remdesivir is showing a positive, promising outcome in different clinical trials. The subsequent successive rate of remdesivir reaches 80 percent [76].

Favipiravir

Favipiravir has unique inhibitory action against RNA-dependent polymerase RNA. Thus favipiravir may have a possible antiviral effect on SARS-CoV-2 (RNA virus) by inhibiting the activity of RNA polymerase [77]. After some clinical trials, it has been confirmed that favipiravir has demonstrated greater antiviral activity than LPV-RTV with substantially light unfavorable effects [71].

Tocilizumab

Tocilizumab is a humanized recombinant, a monoclonal antibody for interleukin-6. This showed promising results in treating individuals with COVID-19 who are seriously or critically ill with coexisting major lung changes and substantially elevated IL-6 levels [71].

Lopinavir-ritonavir

Lopinavir-ritonavir (LPVr) is a mixture of a protease inhibitor and an analog nucleoside. It had previously been used in treating HIV [78]. This protease in vitro interferes with the viral replication [66]. Ritonavir is paired with lopinavir to improve the half-life of their plasmas [79]. The use of LPVr in extreme acute respiratory syndrome was previously tested and suggested a favorable clinical response, decreased viral load at 48 h, and reduced nosocomial infection incidence [78]. It has been confirmed from various clinical trials that, after undergoing treatment for Lopinavir-ritonavir, more than 90 percent of the infected patients showed positive response [79].

Convalescent plasma Therapy

Convalescent plasma, a drug that has gone in and out of fashion for more than a century, but now that infectious disease outbreaks have occurred and have no clear vaccine yet, is increasingly employed [80]. Convalescent plasma which targets the virus directly and the inflammatory response to it remains investigative [81]. Convalescent plasma used to treat COVID-19 across 3 regulatory pathways. For now, they are the only ways to treat patients to receive convalescent plasma, a research medical drug [80].

PREVENTION

Since no therapies for this infection are available at this time, prevention is key. Although antibiotics are ineffective in the treatment of COVID-19 since it is a viral infection and not a bacterial one, some of the worldwide prescribed supportive therapies can be used to avoid COVID-19 if the symptoms worsen. Isolation of confirmed or suspected cases, home ventilation should be perfect with sunshine, patients should be told to wear a clear surgical mask, hand wash with soap, drink plenty of liquids, wear a mask, avoid crowded environments, keep our hands away from mouth, nose and eyes [82].

CONCLUSION

The COVID-19 has pointed out that sex and gender bias with increased cases and deaths in men contrasted with women due to their lifespan, lifestyle factors, sex hormones, sex chromosome linked genes, ACE2 and TMPRSS2, and host immune response to infections. The global health and commercial consequences of COVID-19 has the possible to reach pandemic are severe. At the present time there is no exact choice to preventing COVID-19 or SARS-CoV-2 infection. Without the essential therapeutic interventions, present management is to decrease the contamination rate and keep abetting care for diseased patients. Specially designed clinical trials are urgently needed to develop targeted therapies to reduce the spread of this disease.

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AUTHOR CONTRIBUTIONS

MAI planned and designed the project. MAI, MAM, MLR and MMR performed the literature reviews. MAI, MAM, MLR, MMR, MLK, MAH wrote the manuscript. MAM, MLR, MMR illustrated the figures and table. MAI, MAM and MAH checked and revised the manuscript for necessary changes in format, grammar and English standard. All authors read and agreed on the final version of the manuscript.

CONFLICTS OF INTEREST

Authors declared that they have no conflict of interest.

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Table 1: Trial Report of Some Potential Drugs against COVID-19.

Drug	Trial				Dose (mg/day)	Control	Recovery Rate	Side Effects	Disease Stage	Outcomes	References
	Region	Duration (Days)	Participants (T)	Participants (C)							
Hydroxychloroquine	The Méditerranée Infection University Hospital Institute in Marseille	14	26	16	600	-	70%	-	-	No substantial difference between treated and control patients	[83]
	United States and parts of Canada	-	414	407	600	Placebo		Nausea, loose stools, and abdominal discomfort was the most common side effects	Moderate	-	[84]
Remdesivir	Luigi Sacco Hospital, Milan, Italy	26	35	-	200, 100	-	88.23%	Hepatotoxicity	Mild to moderate	-	[85]
	Hubei, China (10 hospitals)	36	158	78	200, 100	Placebo	98.10%	Constipation, hypoalbuminaemia, hypokalaemia, anaemia, thrombocytopenia	-	Treated patients showed rapid clinical improvement than control patients	[86]
	Wuhan, Hubei Province, China	10	302	151	200, 100	Placebo	-		Severe	Remdesivir is significantly better than placebo	[87]
Favipiravir	Shahid Modarres Medical Education Center and Hospital in Tehran	-	120	120	-	Arbidol	71.4%	-	Moderate to Severe	-	[88]
Lopinavir-ritonavir	Wuhan, Hubei Province, China (Jin Yin-Tan Hospital)	16	99	100	400 and 100	Standard-care	95.95%	Abdominal distress, or diarrhea, loss of appetite, nausea	Moderate to Severe	The treated group showed faster clinical improvement than the control group.	[89]

Figure 1. Classification of SARS-COV-2

Figure 2. Genomic Structure of SARS-COV-2

Figure3. Life Cycle of SARS-COV-2

Figure 4. Sex and age distribution of COVID-19 cases in Bangladesh as of August 31, 2020

Figure 5. Sex and age distribution of COVID-19 deaths in Bangladesh as of August 31, 2020

Figure 6. Male and female of COVID-19 total test, confirm cases, active cases, hospitalizations, ICU cases, recover and deaths in Bangladesh as of 31 August, 2020

Figure 7. Sex Differences in ACE2 and TMPRSS2 regulation

Figure 8. Gender related risk factors and their impact

Figure 9. Transmission of SARS-COV-2

Figure 10. Potential therapeutic treatment of COVID-19