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Conventional and Novel Treatment Strategies to Combat COVID-19 along with Review of most Affected Countries

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Abstract *This review illustrates a comparison of currently implemented strategies and the need of a novel technique to cure the COVID-19. Current strategies served a lot to cope up with the situation by decreasing the rate of fatalities i.e. some FDA approved drugs and giving immunity by the plasma proteins of cured patients, however these approaches could not eliminate the pandemic from the society emphasizing that some advance technology need to be considered in order to fight with SARS-COV-2 virus. CRISPR-Cas based approach to inactivate the virus before its fusion with host DNA has been successful in in-vitro studies performed at Stanford University along with SHERLOCK & MAMMOTH biosciences who were able to degrade 80 % viral genome. Here we have also done a literature review of major affected countries China, Italy, United states, and India.*

Key Words: CRISPR-Cas, Cure, Covid-19, FDA, SARS-COV-2

Introduction

Ever since the man first lay his feet in this world the process of natural selection is going on to keep check and balance between earth resources and the man utilizing them side by side sometimes with natural disasters like floods, volcano eruptions ,earthquakes etc. and sometimes with Epidemic and Pandemic diseases like Cholera ,Influenza ,Typhus, small pox, Measles, leprosy, Polio ,Malaria, HIV and now COVID 19. The 2019 novel coronavirus (2019-nCoV) also known as the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world and affecting a significant world's population. The infection has spread in more than 200 countries and territories [1]. Till 16/10/2020 around 39,418,121 cases of coronavirus disease 2019 (COVID-19) and 1,106,128 deaths have been reported [1]. This review article gives a bird's eye view about the effect of virus on different age groups and gender as well as a comparison of conventional and advanced treatment strategies. Fortunately, children have been least affected by COVID 19, but the future course of this virus is unknown. Data from China, United States, Italy, and India was collected and presented in this review article in tabular or graphical form.

Strategies to Combat COVID-19

To combat COVID-19 numerous strategies are under consideration as well as some are already applied. i.e. around 300 different ways to cope up with this disease and more than 200 vaccines are under clinical trials at various stages, However, traditional approaches look

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like lagging behind the age to fight the SARS-COV-2 even the antiviral therapy. On the contrary Monoclonal antibodies and Vaccination are promising but still many hurdles needed to be passed on. An accurate diagnostic and treatment approach against COVID-19 is far above the current approaches e.g. clinical trials of vaccines on large scale to develop safety & efficacy profile and financial burden on R & D of Antivirals and industrial production hinders the path to eradicate COVID-19.

CRISPR-Cas associated gene editing technology to visualize and then target the genome of corona virus can be a promising lead in this scenario.

Advanced Technique of CRISPR-CAS Based Strategy for Corona

Clustered regularly interspaced short palindromic repeats (CRISPR) and proteins associated with it together constitute a family of sequences of DNA present in certain prokaryotic Organisms in their genomes i.e. bacteria and archaea. Immune system of such pathogens is characterized with these proteins and helps to provide protection against RNA from phages, DNA, plasmids, or other DNA elements that invade their body. Viral genetic material gets destroyed upon binding with a specific target sequence that is present on specific crRNA produced in response to the invasion of foreign substance to the body. Clinical virology has entered a new era by the discovery of this technique to eliminate the RNA and DNA based viruses and even detection and identification of specific sequence of nucleotides is already under use.

SHERLOCK biosciences were able to detect the S gene and *Orf1ab* while MAMMOTH Biosciences did target N and E viral genes facilitating the visual readout of the Corona virus genome [13]. After that many techniques have proven successful to diagnose SARS-COV-2 even in < 40 minutes by the CRISPR based lateral flow assay. CRISPR/Cas-NER assay demonstrated 100 percent agreement with PCR in diagnosis of COVID-19 with the success probability of p <0.001.

In a recent study [14], researchers were able to degrade 80-90% of the genetic material of SARS-CoV-2 using a pool of Cas13d (RNA Targeting CRISPR from Class II) and crRNA by targeting multiple regions on the genome of coronavirus. This Technology was coined the name PAC-MAN (Prophylactic Antiviral CRISPR in huMAN cells). It led to the fact that a pool of 6 crRNA could target all the strains of Coronaviruses.

Selective and Efficient Delivery of CRISPR-Cas13 in Antiviral Therapy

The main obstacle in the application of this technique is the delivery of the components of CRISPR to the viral genome. Current method to deliver the CRISPR is non specific means target the both infected as well as normal cells that can cause harmful side effects even in the absence of Viral RNA. Thus there must be some methods that can deliver strategically CRISPR components in to the infected cells only before the testing of this techniques on human level.

One way is to synthesize Cas13 nuclease in such way to have affinity with the viral particles, hence it will deliver the CRISPR components specifically and efficiently into the host cell upon the entrance of the virus itself. In this way the delivery of the virus and the treatment will follow the same path. CRISPR-cas complex will shred the RNA of the virus when it will be released into the host cell cytoplasm by the virus, so the Viral RNA will be cleaved before its translation and replication inside the host cell nucleus. Hence the virus itself will be the main key to kill itself selectively and efficiently.

COVID-19 by Area, Age and Gender

The COVID 19 infection which is affecting a significant world's population is an emerging global health concern. The infection has spread in more than 200 countries and territories affecting more than 12 million people till now. Data from some of the countries were collected and presented in this article in tabular or graphical form.

China

Wuhan the city of China was the place where the virus started spreading. It was identified in December 2019 in Wuhan however the first case traced back to November 17, 2019.

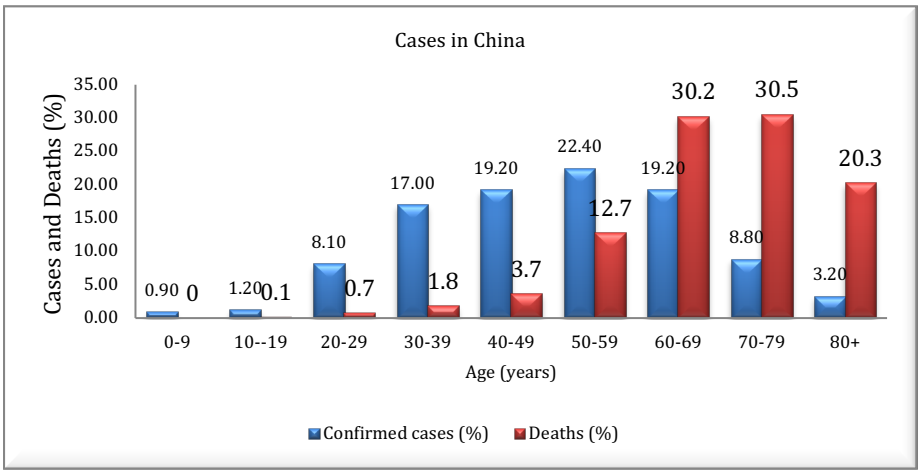

Figure 1: Graphical Representation of Number of Cases and Deaths within Different Age Groups in China

According to WHO COVID 19 dashboard data, there was an almost linear relationship between total COVID 19 cases and the number of new reported from April till July. The initial spread was very fast making the number in December from a few hundred to the end of January at almost 12,000 and then at the end of February, there were 79,000 cases after that the spread is limited. There were 84,784 COVID 19 cases in China until 25 July.

A total of 72,314 individuals were diagnosed with COVID-19 as of February 11, 2020. 44,672 cases (61.8%) were the confirmed cases, 16,186 cases (22.4%) were suspected, 889 cases (1.2%) were asymptomatic, and 10,567 cases (14.6%) were clinically diagnosed(Zhi, 2020). Most numbers of patients were 30 to 79 years of age (87%), 10 to 19 years of age were (1%), and 3% were age 80 years or older. Most of the cases were diagnosed in Hubei (75%) and most Wuhan related exposures (86%) [2]. Among 44,672 confirmed cases in China, 22,981 (51.4%) were the males and 21,691 (48.6%) were the females. The male to female ratio was 1.06:1 in China overall while in Wuhan it was 0.99:1 [3].

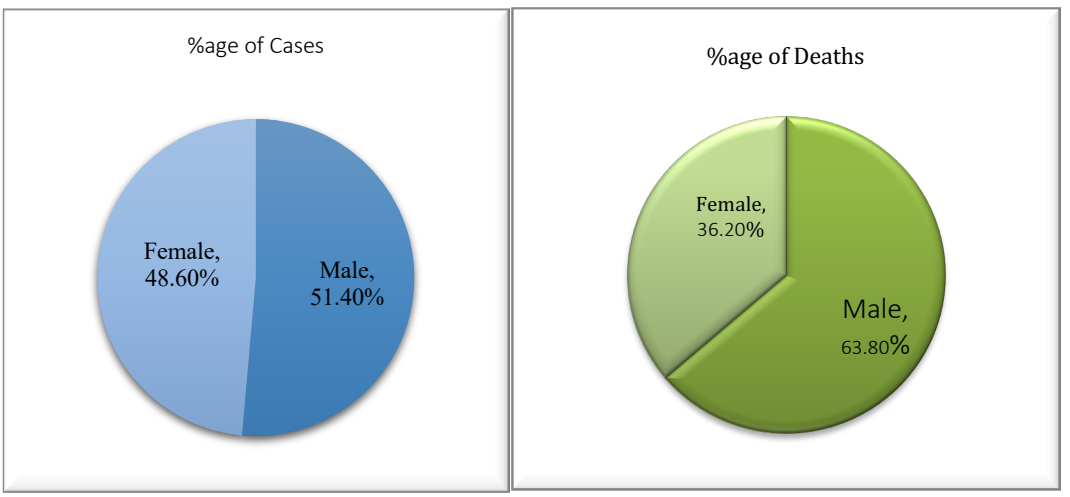

Figure 2: Comparison of Percentage of COVID Cases and Deaths among Males and Females of China

United States

A study was conducted which was published in JAMA (The Journal of American Medical Association) on April 15, 2020, in which they had studied that almost more than 50% cases were from the Chicago and in those 50% the percentage of the deaths accounted for more than 70% of black people, although blacks were almost 30 percent of the total population.

In Louisiana, 70.5 percent of deaths accounted for black people who represent 32.2 percent of the state population

The Johns Hopkins University and American Community Survey indicated that out of 131 predominantly black people regions in the USA the infection rate was 137.5 out of 100,000 people simply 0.1375% and the death rate was 6.3 out of 100,000 people which was 0.0063%.

The World Health Organization declared the COVID-19 outbreak a pandemic on March 11, 2020. Among the 1,761,503 cases reported to CDC from January 22–May 30, individual case reports for 1,406,098 were submitted to CDC case surveillance.

Table 1. Percentage of Covid-19 Cases within Different Age Groups

Age Group (yrs.)	No. of Cases	Percentage
0-9	20,458	1.5
10-19	49,245	3.7
20-29	182,469	13.8
30-39	214,849	16.3
40-49	219,139	16.6
50-59	235,774	17.9
60-69	179,007	13.6
70-79	105,252	8
80+	114295	8.7
All Ages	1,320,488	100.0

After exclusions, data for 1,320,488 (94%) cases were analyzed. The following table shows the number of patients affected by COVID 19 with different age groups [4].

The spread of COVID 19 in the United States was slightly greater in females as compared to males. Among 1,320,488 of total analyzed cases, 646,358 of them were the males and 674,130 were the females. But the number of deaths in males was greater than in females. 38,773 out of 646,358 were the reported deaths in males and that is about (6%) while on the other hand 32,343 out of 674,130 were the reported deaths in females and that was (4.8%) [4].

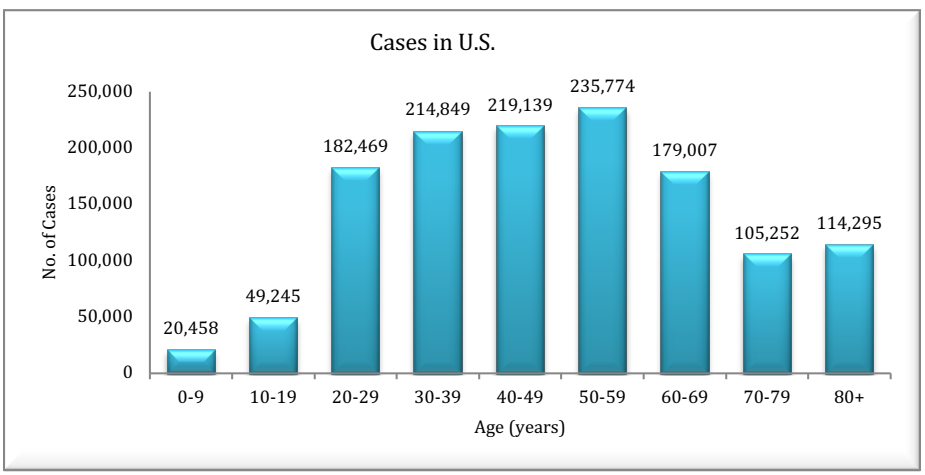

Figure 3: Graphical *Representation* of no of *Cases* within *Different Age Groups* in United States

Table 2. Number of Cases and Deaths among Males and Females in United States

Sex	No. of Cases	Deaths	Deaths (%age)
Males	646,358	38,773	6.0
Females	674,130	32,343	4.8

Italy

Italy being the part of Europe was also not safe from the terrorizing effects of COVID 19, till February 2020 there were only 3 cases of COVID 19 and all of those which were traveled to china recently on February 2020 a person with aggravated pneumonia due to COVID 19 was diagnosed in northern Italy Lombardy region who was in his 30s and had no history of abroad within 2 weeks many other cases were reported then it was hypothesized the virus was in population since January 2020 but became active in February 2020 [5].

Due to increasing number of cases the Italian Ministry of Health issued some policies, according to these policies the patients who have more clinical symptoms have undergone the tests of COVID 19 and people who have mild symptoms and asymptomatic were left despite accounting for a limited number of tests, there was a high portion of positive results about 19.3% (positive cases 21,157 of 109,170 tested as of March 14, 2020) also the case fatality rate changed from 3.1 % on February 24, 2020, to 7.2 % on March 17, 2020, because the mild symptoms cases and asymptomatic cases also add their share in fatality percentage after that almost all patients have shown symptoms whether mild or severe undergone testing [5].

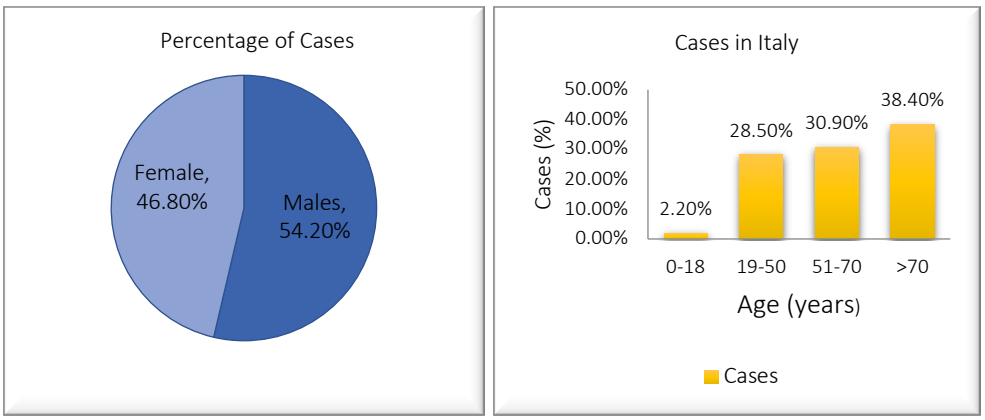

Figure 4: Graphical Representation of Number of Cases Among Various Age Groups in Italy

The overall case fatality rate in Italy (7.2%) was three times more than China (2.3%) and that increasing number was from the people in Italy who were more than 70 years whereas in China the death rate in people above 70 years of age was not as much as in Italy and the possible reason can be genetic makeup and environmental conditions. Chinese people eat more natural foods thus have a strong immune system which can bypass the virus attack [5].

According to the data collected there were 22,512 active cases in Italy till March 15, 2020 [6], the number increased to 105,792 on April 1, 2020, (2) and according to WHO COVID 19 dashboard data there were 238,159 cases till June 20, 2020 and the numbers were 245,590 cases until July 25, 2020.

According to Istituto Superiore di Sanità Italy has 235,579 confirmed cases of COVID-19 and 32,722 associated deaths as of June 8, 2020. The median age of cases is 61 years, and more than two-thirds of these patients had diabetes, cardiovascular diseases. Of the patients who died, 38.4% were aged >70 years, 30.9% were aged 51 to 70 years, 28.5% were aged 19-50 years, and 2·2% were aged 0-18 years [7].

Table 3. Percentage of Deaths and CFR Among Various Age Groups in Italy

Age (years)	No. of Deaths	% of Deaths	CFR*
0-9	4	0	0.2%

Age (years)	No. of Deaths	% of Deaths	CFR*
10-19	0	0	0%
20-29	15	0	0.1%
30-39	64	0.2	0.3%
40-49	282	0.9	0.9%
50-59	1,141	3.5	2.7%
60-69	3,335	10.2	10.6%
70-79	8,738	26.7	26%
80-89	13,384	40.9	32.6%
>90	5,759	17.6	30.4%
Total	32,722	100	13.9%

The spread of coronavirus in Italy was slightly greater in females as compared to males. As the chart shows, 54.2% were the females and 46.8% were the males. As of May 26, 2020, a study on 32,000 patients revealed that the fatality rate is much higher for men. If the mortality rate for female patients was 10.4% the mortality rate for male patients was 17.7% [8].

India

The first case reported in India was on Jan 30, 2020. As of June 16, 2020, India had a total of 344,407 confirmed cases of coronavirus and 9,921 deaths(*Coronavirus | 42% of patients in India between 21 and 40 years*, 2020). The Union Health Ministry on April 4, 2020, throwing light for the first time on the demography of the cases in India, and according to that, about 42% of confirmed COVID-19 in India ware between the ages of 21-40 years old. The percentage of those who were over age 60 was only 17%. The U.S. Centers for Disease Control said that 29% of the affected were the age of 20-44 years and 32% were above 60 years. The United States recorded the 279,355 cases and 7,451 deaths compared to the 2,904 cases and 75 deaths as on April 4, 2020 [9].

India Today's Data intelligence Unit on 3rd April 2020 showed 1801 COVID-19 confirmed cases revealed that around 60 percent of the patients were below 50, so young Indians were at higher risk to get this disease as compared to other population. Similarly, data also revealed that 17% of the patients were in their 40s, 21% (376 cases) were in their 20s and 22% (391 cases) were in between 30 and 39 years of age. [10].

Early reports from countries, such as China and Italy, have shown that the most vulnerable category affected by COVID-19 is that of older people. But in India, patients over the age of 60 were only 19% of the total confirmed cases while people aged 80 and older account for less than 2% of the total confirmed cases of COVID-19 [11]. The CFR (Case Fatality rate) among males was 2.9%, while that for females it was 3.3% in India. As of May 20, 2020, 66% were the males affected by COVID-19 infection while 34% were the females.

Conventional Strategies to Treat COVID-19

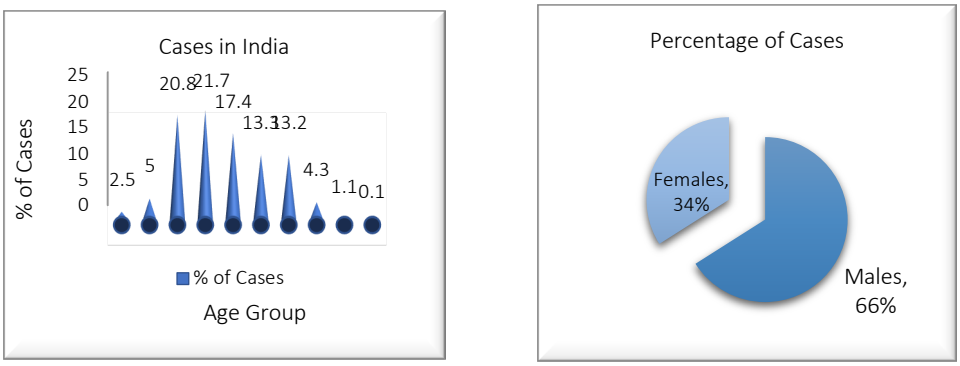

Figure 5: Graphical Representation of %age of cases in *different age groups* in India

Limitations

Our study has some limitations as only those countries were included in the study that were most affected while those countries who had minor impact were excluded from the study. Hence the results interpreted including the variation of cases among different age groups and among gender are based on four countries China, Italy, United States and India.

Secondly the application of CRISPR-Cas although looks promising but still itself is a barrier to be implemented on large scale as In-vivo studies and Clinical and Pre-Clinical trials will cost much time and finance.

Conclusion

The future trajectory of this virus is still not clear. From the data, it can be concluded that most of the patients were 30 to 70 years of age. Age is one of the important factors playing a key role in the progression of COVID 19. Different countries have different ratios of young to old age persons. The recovery rate is also higher in countries with a high number of young people as compared to those with a high number of old people. The least affected age group in the world is 0 to 20 years of age. On the other hand, cases in males in China, Italy, and India are more as compared to females while in the United States, females are more affected by COVID 19. Different countries and organizations of the world are trying to discover the treatment of COVID-19 but nobody has succeeded to discover the effective drug or vaccine against this rapidly spreading virus. One of those approaches is targeting the genome of coronavirus by applying CRISPR-Cas associated gene-editing technology.

In the scientific community CRISPR can be a very crucial and important area of research study to explore the disease diagnosis as well as treatment in the future with promising potential. Using this technique, we can develop such Novel drugs to cure a range of diseases for example Alzheimer's, HIV/AIDS, Cancer, HIV and such pandemics like Covid-19.

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