

REVIEW ARTICLE

History and Spread of Viruses (COVID-19) and Associated Demographic and Clinical Parameters – A systematic review and meta-analysis

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Abstract

COVID-19 made a huge impact on the world due to its rapid transmission and no treatments being available for it. The virus affected more people and spread to various countries than what was predicted when COVID-19 initially began spreading. There have been numerous pandemics and epidemics in the 21st century yet COVID-19 has affected more people and spread widely. The primary objective of the study was to explore history, spread and associated parameters of existing viruses especially COVID-19. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed for a systematic search to identify eligible published articles. Clinical data, regarding COVID-19 patients, was obtained from previously published articles. The main cause of COVID-19 spreading rapidly was noted to be due to a high percentage of asymptomatic patients, transmission being air-borne, and the lack of knowledge and preventative measures being implemented when the virus began spreading. The common co-morbidity that found in patients was Diabetes Mellitus, Hypertension, and Coronary Heart Disease. The common symptoms, found through the Meta-analysis, that the patients faced included cough (55.4%), fever (68.4%), fatigue (20.3%), and shortness of breath (18.1%). The proportion of asymptomatic positive cases was measured 58.3% (95%CI: 24.7% – 87.9%) while mortality proportion was found to be 6.7% (fixed-effect model) and 13.4% (random-effect model). The Meta-analysis indicated that a higher percentage of males were affected by COVID-19 than females and more patients are found to be asymptomatic. Moreover, the mortality rate of patients that have had COVID-19 was found to be low.

Keywords

Covid-19; Spread; Transmission; Asymptomatic; Co-Morbidity; Symptoms; Mortality

Introduction

The novel coronavirus pandemic, COVID-19, has become a concerning health emergency for the world due to its rapid and prevalent spread. As of 19

July 2020, there have been over 14 million confirmed cases reported accompanied by 597,583 deaths from over 200 countries.(1) The virus was first identified as numerous patients from Wuhan, China were

diagnosed with pneumonia in December 2019, and then in March, the World Health Organization (WHO) declared COVID-19 a pandemic.(2) The virus primarily spreads from human to human transmission and numerous studies have proposed that the virus has the capability of spreading during the incubation period of 14 days.(3) The transmission of the virus takes place through respiratory droplets that are released when coughing and sneezing. The virus enters the body through either the mouth, eyes, or nose and has caused severe pneumonia and led to death in several patients.(4)

The COVID-19 pandemic has been hard to contain due to several factors like the presence of asymptomatic patients, chances of transmission during the incubation period, a relatively high reproduction number (R0), and the lack of education regarding social distancing norms. The most effective method of controlling the outbreak is preventing human to human transmission which can be achieved via implementing social distancing and hygiene norms.(5) This has led to multiple countries and cities following lockdown or curfew conditions to flatten the curve formed by recording the spread of the virus.

Aims & Objectives

Multiple viruses have caused either a pandemic, epidemic, or an outbreak in the 21st century, yet, COVID-19 remains to be one of the most contagious and widespread pandemics that the world would have witnessed. COVID-19 may not be as fatal as MERS or SARS, but it has impacted more areas and a higher population across the globe. A question that arises from COVID-19's vast and speedy spread is the reason that the virus has had a greater impact on a larger proportion of the population in comparison to the outbreaks that came before COVID-19. This review aims at summarizing different factors of COVID-19 that have allowed to become a widespread pandemic in comparison to previous outbreaks like SARS, MERS, Zika, H1N1 (Swine flu), H1N1 (Spanish flu), and Ebola. Furthermore, the review aims at analyzing the clinical characteristics of COVID-19 through a systematic review and meta-analysis.

Material & Methods

A rapid review for a broad range of COVID-19 following a standardized guideline i.e. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was conducted.(6) A systematic

literature search of electronic databases (PubMed, Scopus, Cochrane, and Google scholar) was done using keywords COVID-19 (including all mesh terms), symptoms, co-morbidity, and death (mortality). A Systematic literature search in electronic databases was done for Dec 2019 to July 2020 using Boolean operation with combinations of the search terms: "COVID-19 OR COVID19 OR COVID-19 pandemic OR SARS-CoV-2 infection OR COVID-19 virus disease OR 2019 novel coronavirus infection OR 2019-nCoV infection OR coronavirus disease 2019 OR coronavirus disease-19 OR 2019-nCoV disease OR COVID-19 virus infection AND Symptoms AND Co-morbidity OR Comorbidity AND Death OR Mortality AND Asymptomatic".

In addition, the reference lists of each eligible publication were carefully checked in order to identify additional records. Two-three authors independently read the full manuscript and judged on the basis of inclusion and exclusion criteria to include it in the present systematic review. In case of any disagreement, Delphi Method was used to resolve the issue. Quantitative data synthesis was used for included studies that are sufficiently homogenous in nature. The aim of the initial broad search was to identify all COVID-19 scientific and medical literature to answer a range of research questions related to demographic and clinical outcomes. We followed a strict criteria (Dec 2019 onwards) to select references which contain demographic and clinical outcomes related to COVID-19 and removed various articles from the search due to the proliferation of COVID-19 literature.

MedCalc Statistical Software version 19.2.6 (MedCalc Software by, Ostend, Belgium; <https://www.medcalc.org>; 2020) was used for meta-analysis. Random effects model was considered more appropriate, in which both the random variation within the studies and the variation between the different studies are incorporated. This assumption was tested by the "Heterogeneity test". If this test yields a low P-value ($P < 0.05$), then the fixed effects model may be considered invalid. I² statistics with 95% Confidence Interval (CI) was used to show the percentage of inconsistency.

Results

A total of 25 studies were included and a selection of studies was presented in (Figure 1). The total sample size was observed 55420 subjects with a

pooled average age of 52.7 ± 3.1 years ranging from 46.7 – 58.8 years (95%CI) (Figure 2). (Figure 3) shows the forest plots for proportions of gender. It is observed that 52.6% male and 47.4% female were diagnosed with COVID-19 and the difference in proportion was found statistically significant ($P < 0.001$) as the sample size was large.

17 studies out of 25 discussed about co-morbidities (Figure 4). 53.8% (95%CI: 41.1% – 66.3%) subjects in these studies were having co-morbidities. 11 studies showed number of events about some common co-morbidities such as Hypertension (HT), Diabetes Mellitus (DM), and Coronary Heart Disease (CAD). (Figure 5) reveals pooled proportion of HT ($p=29.2\%$; 95%CI: 10.8 – 52.1), DM ($p=15.3\%$; 95%CI: 10.3 – 21.0), and CAD ($p=11.0\%$; 95%CI: 6.8 – 16.2).

(Figure 6) depicts forest plots of the proportion of asymptomatic subjects in eight studies. 58.3% (95%CI: 24.7% – 87.9%) of the study subjects were asymptomatic or not having any symptoms at the time of diagnosis of COVID-19.

Furthermore, 17 studies mentioned mortality due to COVID-19. (Figure 7) reveals that 6.7% (fixed-effect model) and 13.4% (random-effect model) was the pooled mortality percentage. However, none of the studies were found to be discussing the survival rate as almost most of the studies were cross-sectional studies.

Funnel plot for assessing publication bias based on study proportions is shown in (Figure 8). Circles indicate study point estimates. There was no clear asymmetry found and therefore, funnel plot demonstrates no significant publication bias.

Discussion

(Table 1) depicts the comparison of origin, spread, transmission, and WHO recommendation for pandemic viruses such as H1N1 (Spanish Flu), Zika, Ebola, SARS, H1N1 (Swine Flu), and MERS with the COVID-19 virus. No treatment or vaccine is still available till date to fight against these viruses.

Multiple viruses have caused either a pandemic, epidemic, or an outbreak in the 21st century, yet, COVID-19 remains to be one of the most contagious and widespread pandemics that the world would have witnessed. COVID-19 may not be as fatal as MERS or SARS, but it has impacted more areas and a higher population across the globe. A question that arises from COVID-19's vast and speedy spread is the reason that the virus has had a greater impact on a larger proportion of the population in comparison to

the outbreaks that came before COVID-19. This review aims at summarizing different factors of COVID-19 that have allowed to become a widespread pandemic in comparison to previous outbreaks like SARS, MERS, Zika, H1N1 (Swine flu), H1N1 (Spanish flu), and Ebola.

Spread and Transmission: A systematic review adequately explained that Corona-viruses are large, lipid-enveloped, single-stranded RNA viruses found in avian and mammalian species. The review made the authors question why COVID-19 transmitted globally, when compared to other viruses. It is the fact that COVID-19 spread around the world far quicker than originally predicted. The article published in Lancet medical journal confirmed that Wuhan's first known COVID-19 patient began developing symptoms in December 2019. The World Health Organization (WHO) declared the COVID-19 epidemic a global health emergency in January.

In Japan, more than 3,700 passengers from 48 countries were quarantined on a cruise, called Diamond Princess after a passenger who departed in Hong Kong was found to be a confirmed and asymptomatic patient of COVID-19(7). COVID-19 appears to have a fatality rate of 4.4%, which is much lower than the 10% fatality rate for SARS and approximately 30% for MERS-CoV. Nevertheless, COVID-19 is found to be more contagious than SARS or MERS-CoV, and critically it spreads undetected.(8) At the beginning of 2020, it was unclear whether or not asymptomatic COVID-19 patients had the ability to transmit the virus. Numerous studies indicate that the virus particles are present in the saliva of COVID-19 patients and thus asymptomatic patients have the capability of transmitting the virus. Though the possibility of transmission before symptoms develop seems to be infrequent, there are suggestions that asymptomatic individuals could transmit the virus.(9) Limited studies and data are available for asymptomatic infections.(10)

In a recent study,(11) an immense number of total infections were estimated out of which undocumented (80% to 90%) cases and undetected infections were the sources for 79% of documented cases in China.

However, a study reveals that asymptomatic cases are assumed half as infectious as symptomatic ones (relative infectivity $f_a=0.5$). (12) COVID-19 infections are often not accompanied by symptoms. The most reported symptoms include mild flu, cough, fatigue, and headaches.(13) A review study shows that there

is some evidence that patients may not be infectious for the whole period that they are SARS-CoV-2 (COVID-19) positive and that infectivity may be related to the viral load and time since symptom onset.(14)

Prevention and treatment: To date, no drugs are currently approved for COVID-19 although some have been tried such as Chloroquine and hydroxychloroquine. Two small human studies have been conducted with both these drugs in COVID-19, and have shown significant improvement in some parameters in patients with COVID-19.(15,16,17,18,19)

The term 'household isolation' refers to households going into isolation for a fixed duration of time. This approach reduces the risk that other household members would transmit in the community when patients are pre-symptomatic or if they are asymptomatic but still infectious.

Social distancing is the policy widely adopted in many countries to limit transmission of SARS-CoV-2 (COVID-19), at a great economic and social cost. Social-distancing policies may have an important role in mitigating the spread of pandemics; for many infectious diseases, such as influenza.(20) Multi-site screening including nasal and pharyngeal swabs, stool, and sputum specimens could be considered to improve the diagnosis, treatment, and infection control in patients with COVID-19.(21)

The purpose of the study has been to understand why COVID-19 has proven to be a widely spread virus across the globe. COVID-19 has been established to be less deadly than the viruses that have caused other pandemics, yet it is more contagious.(3) The COVID-19 virus can easily transmit from one person to another through the air, respiratory droplets, or contaminated surfaces, and the virus can go unnoticed in asymptomatic patients making detection very difficult.(4,13,14)

Another important aspect that leads to the virus spreading so rapidly was the lack of knowledge that was present when the virus first crossed over from animals to humans.(8,22) This meant that at the early stages there was not adequate medical protection, social distancing measures, protective measure, and awareness in the general public which permitted the virus to infect numerous people.(23)

The Meta-analysis permits for the evaluation of clinical characteristics of various COVID-19 patients. Through the results it can be derived that 58.3% of COVID-19 patients were asymptomatic which was

found using eight studies that had clinical data regarding asymptomatic patients and confirmed by the published studies.(10) A high percentage of asymptomatic patients along with risks of transmission allows for the virus to spread in a larger percentage of the population, going unnoticed.(24,25,26,27,28,29,30,31,32)

There was a slight difference between the proportion of male and female patient's data, indicating that there may be more males that are affected by the virus than females. Certain studies suggest that women are less susceptible to the virus due to the presence of the X chromosome and certain sex hormones which allow for the development and strengthening of adaptive immunity. (32) Further exploration of immunity between males and females who get impacted by COVID-19 needs to be carried out to establish the difference. (7,10,20,22-31,33-45) The common symptoms, found through the Meta-analysis, that the patients faced included cough (55.4%), fever (68.4%), fatigue (20.3%), and shortness of breath (18.1%). (7,10,20,22-28, 30, 31, 33-45)

Co-morbidities weaken the immune system of a person, which then allows the COVID-19 virus to have a severe impact and cause further complications to the patient. (22,25,26,28,29,30,40,44,45) The common co-morbidity that was found in patients was Diabetes Mellitus, Hypertension, and Coronary Heart Disease (7, 10,20,22-29,30,31,33-45). The death rate for a patient that has co-morbidities and gets infected by COVID-19 are higher than a healthy patient. (7,10,22,24,26,28,29,31,36,37,38,40,42,44,45)

Conclusion

This systematic review and meta-analysis found that the evidence suggests that the viral load of COVID-19 is more on males as compared to females. However, the clinical significance of this finding is indecisive. There is some evidence that more patients are found asymptomatic in nature. The study revealed a low mortality percentage due to COVID-19. However further studies are required to measure pure percentage of death with or without co-morbidity to understand the seriousness of the disease. It is noted that due to the highly fluid, dynamic, asymptomatic patients, the evolving nature of the pandemic, and the describing natural history of the disease process it spreads globally.

Limitation of the study

The current study has a few limitations. In our study, a high degree of heterogeneity was observed; however, we did not find the sources of heterogeneity in our analysis. The observed heterogeneity might be due to the population characteristics, most of the studies were published on the Chinese population. However, heterogeneity was minimized by using a random effect model of analysis. Further, the quantity of the number of studies available on COVID-19 was large enough to assess the quality of study hence we focused only on studies discussing demographic and clinical parameters. In addition, we tried to reduce selection bias by using stringent searching strategy.

Relevance of the study

This review allows for a better understanding of the spread of COVID-19 when compared to other pandemics and epidemics that have occurred. It lays out a comparison and analyzes clinical characteristics of COVID-19. Understanding the clinical characteristics can permit for a better understanding of the pandemic and its reaction on different patients.

Authors Contribution

SA: Literature search, data extraction, manuscript writing, SS: Critical review of included full articles and manuscript writing and reviewing, SA: Critical review of included full articles and manuscript writing, SMA: Critical review of included full articles and manuscript writing, RS: Data extraction, submission and coordination with authors, GV: Conceptualization, Literature search, data extraction, Methodology, manuscript writing

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Tables

TABLE 1 HISTORY, SPREAD AND TRANSMISSION OF THE VIRUSES

Virus	Place of Origin	Year	Spread	Transmission	Reasons that virus did not spread as much as COVID-19	WHO initiative/ comment for controlling the spread	Reference #
H1N1, Pandemic, Spanish Flu	Not Known believed to be from China, France, Britain, or USA	1918	<ul style="list-style-type: none"> • After world-war-1, the H1N1 Spanish Flu was the deadliest pandemic that the world faced. • Estimates suggest that the pandemic resulted in the death of almost one-third of the world's population with approximately 40 million deaths(46). • The pandemic affected US, Europe, and parts of Asia. Studies also indicate that the pandemic resulted in deaths amongst young adults, which is unusual as most strains of influenza do not have a severe impact on their age group (46). • In US the pandemic came to an end by the summer, as the weather did not favor the virus, and by this time people either developed immunity or had died(47). 	<ul style="list-style-type: none"> • In 1918, due to the lack of scientific and medical advances, very little was known about the H1N1 Spanish Flu virus. The genome of the virus has been sequenced in modern-day, using the fixed and frozen lung tissue from a 1918 influenza victims(48). The host of the H1N1 1918 influenza has not been identified(49). • The transmission of the virus has not completely been understood and a few research studies suggest that the influenza virus transmits in a similar way to the common cold virus. • The human-to-human transmission is believed to occur via the following: <ul style="list-style-type: none"> ○ Respiratory droplets from coughing and sneezing ○ A patient contaminating inanimate object and surfaces ○ Inadequate protection at the healthcare setting 	<p>Since very little is known about the H1N1 virus that caused a pandemic in 1918, comparing it to the current COVID-19 virus is difficult however with suggestions found from research the following can be suggested:</p> <ol style="list-style-type: none"> 1. People began to develop immunity to the H1N1 virus <ul style="list-style-type: none"> ○ Studies suggest that the reason that the 1918 virus had very little impact on the elderly population was that they had some immunity to the virus from the 1847 pandemic(49). ○ As more people got infected with the virus and recovered, they had immunity from the virus(49). ○ With COVID-19, WHO states that there are currently no studies that verify that patients who have recovered from COVID-19 have immunity from a second infection(50). 2. The H1N1 virus was very lethal and resulted in numerous deaths. <ul style="list-style-type: none"> ○ The death of a patient meant a decrease in the population and decreased the chance of the virus spreading further ○ It is suggested that one third of the population died from the H1N1 pandemic in 1918(51). 3. International Travel was not as advanced in 1918. <ul style="list-style-type: none"> ○ Globalization has connected the world and advances in aviation have interconnected the world. The movement of people from one country to another allows for imported cases. ○ In 1918, travel was limited and that prevented the H1N1 virus 	N/A	[46], [47], [48], [49], [50], [51]

					from spreading in all continents of the world.		
ZIKA	Uganda and The Republic of Tanzania(7)	1952	<ul style="list-style-type: none"> • There have been numerous spreads and outbreaks of the Zika virus. The largest outbreak occurred in 2007 on the island of Yap (53). During which approximately 5000 people were infected and it lasted for three months. • In 2013, there was a big outbreak that occurred in the French Polynesia. The virus spread eastwards toward Oceania and then to South America (54). There were approximately 20,000 people infected. • In 2015, there was an outbreak that began in Brazil and it spread to nearly 50 countries. This outbreak was declared an epidemic. 	<ul style="list-style-type: none"> • The Zika virus is transmitted when the Aedes genus mosquito infected with the Zika virus bites a human. • Human-to-human transmission can occur via the following (55): <ul style="list-style-type: none"> ○ Pregnant women infected with the Zika virus can pass the virus to the fetus and it has been noticed that the babies that get infected during pregnancy can have birth defects like microcephaly (55). ○ Transmitted through sexual contact with an infected person. ○ Blood transfusion of an infected patient. ○ The blood of an infected person comes in contact with another person. ○ The incubation period of the virus is 3-14 days. Most people who get infected with the Zika virus generally do not develop major symptoms and the symptoms are generally mild (54). These symptoms last for 2-7 days. 	<ol style="list-style-type: none"> 1. The mode of transmission for the Zika Virus is the mosquito (55) <ul style="list-style-type: none"> ○ Using mosquito repellents and staying in places that do not have mosquitoes can prevent a person from getting the virus. ○ The COVID-19 virus mainly spreads from human-to-human transmission, and hence social distancing is the most important aspect in preventing it from spreading. 2. The human to human transmission in Zika Virus does not occur easily(56). <ul style="list-style-type: none"> ○ When a person has the Zika virus they can only transmit it to another person when their blood comes in contact with another person. ○ With COVID-19, respiratory droplets are the main mode of transmission. This makes the COVID-19 virus more contagious and allows it to spread easily. ○ COVID-19 has asymptomatic patients and it can spread during the incubation period. 4. Zika virus can either be transmitted from a mosquito or an infected person's body fluids <ul style="list-style-type: none"> ○ COVID-19 can go undetected in an asymptomatic patient and it can be transmitted to others. 	<p>There are no vaccines or treatments available for the Zika virus and hence supportive care is recommended.</p> <ul style="list-style-type: none"> • Protection against mosquito bites during the day and the evening by using mosquito repellents that contain DEET, IR3535, or icaridin. • Wearing clothing that covers most of the body and wearing light colored clothes to prevent mosquito bites • Physical barriers should be used like closed windows and doors. • Sleep under the mosquito nets. • Avoid sexual contact with people who are infected with the Zika virus. 	[52], [53], [54], [55], [56]
Ebola	Near the Ebola River in Democratic Republic of Congo (formerly known as Zaire)(12).	1976	<ul style="list-style-type: none"> • There have been 26 outbreaks of the Ebola Virus Disease to date. The first two were consecutive outbreaks that occurred in Central Africa. This was the deadliest outbreak with 218 deaths out of the 318 patients that were infected (57). 	<ul style="list-style-type: none"> • The virus is transmitted from human to human through blood, bodily fluids, and being in contact with people who are infected or have died from the Ebola Virus Disease (58). • The Ebola Virus Disease made the spillover to humans through a infeced non-human primate via direct contact of secretions, organs, bodily fluids, or blood (59). • There is no evidence that suggests that Ebola virus can be transmitted through skin-to-skin contact or through small 	<ol style="list-style-type: none"> 1. Ebola Virus cannot be transmitted during the incubation period, whereas research shows that COVID-19 can be transmitted during the incubation period (59). <ul style="list-style-type: none"> ○ Ebola virus disease can only be transmitted through bodily fluids or blood whereas COVID-19 spreads through the small droplets that a person lets out during coughing or sneezing. This makes COVID-19 more contagious. 	<ul style="list-style-type: none"> • Reducing the contamination of wildlife-to-human transmission. • It is advised to minimize contact with non-human primates as well as avoid the consumption of their raw meat. • Reduction of human-to-human transmission. • The patients that are infected and have died need to be buried properly to prevent 	[57], [58], [59], [60]

			<ul style="list-style-type: none"> The other significant breakout took place between December 2013 to June 2016 and it was the largest spread. The affected areas included Guinea, Liberia, and Sierra Leone²³. There were over 26,000 cases detected. 	<p>droplets that are released when coughing and sneezing (58).</p> <ul style="list-style-type: none"> The incubation period of the virus is 2 to 21 days and the virus cannot spread during the incubation period (59). 	<ul style="list-style-type: none"> Certain studies regarding COVID-19 suggest that airborne transmission is possible (60). 2. Symptoms of the Ebola Virus are distinct and early detection is possible whereas for COVID-19 the symptoms are similar to a common cold in the first few days of appearing making detection more difficult. 	<p>transmission of the virus from the dead body.</p> <ul style="list-style-type: none"> Sexual transmission is possible and hence awareness needs to be spread. Recovered patients need to be advised to practice safe sex for 12 months after the appearance of their symptoms as studies suggest that the virus can be present in the semen (60). Pregnant women infected with Ebola Virus can have the virus present in their milk even after they have recovered. 	
SARS	Guangdong, China	2002	<ul style="list-style-type: none"> The SARS outbreak began in November 2002 in the Guangdong province in China (61): 26 countries were impacted by the outbreak and there were over 8000 cases reported. Due to its large impact and spread it was announced to be a pandemic by WHO. The spread of the virus from China to other countries was found to be due to imported cases. SARS caused the death of nearly 1800 people in China. The first outbreak that began in 2002, ended in 2004 and no more outbreaks of SARS have occurred after that. WHO had declared Guangdong to be a zone where re-emergence of the virus can occur. 	<ul style="list-style-type: none"> The spillover of the SARS virus is believed to be from an animal reservoir, though the animal species has not been identified yet but believed to be a bat (62). Most transmission of the SARS virus occurred through person-to-person contact. <ul style="list-style-type: none"> Respiratory droplets of infected people produced when coughing and sneezing. The virus can spread through objects that can get contaminated by an infected person. Stool of an infected person. Inadequate prevention and control in the healthcare setting. 	<p>1. Studies suggest that SARS does not spread during the incubation period (63).</p> <ul style="list-style-type: none"> COVID-19 spreads during the incubation period which makes the virus more contagious and makes prevention harder. There are many patients of COVID-19 that are asymptomatic, which allows them to go undetected and spreads the virus further (64). <p>2. The reproduction number, R₀, for SARS is found to be under 1, in isolation, but the median R₀ is found to be between 2-4 (65).</p> <ul style="list-style-type: none"> COVID-19 has an R₀ that ranged between 2-2.5. <p>3. COVID-19 has asymptomatic and the virus spread during the incubation period, which overall makes it harder to track and allows the virus to spread from one person to another even before the original patient can be diagnosed with the virus (64).</p> <p>4. Besides SARS being a big pandemic of the 21st century there are no treatments available to help patients.</p>	<p>At present there are no vaccines or FDA approved treatments that are available for SARS-CoV and supportive care is recommended.</p> <ul style="list-style-type: none"> Provide healthcare workers with adequate protective gear to prevent the transmission from patients to healthcare workers Wash hand and maintain proper hygiene Promote testing and isolation of infected patients Avoid contact with animals and do not consume undercooked or uncooked meat 	[61], [62], [63], [64], [65]

<p>H1N1, Swine Flu</p>	<p>Mexico</p>	<p>2009</p>	<ul style="list-style-type: none"> • The first case of the novel H1N1 appeared in Mexico in 2009 (48). By June of 2009, WHO had declared the outbreak of H1N1 virus that caused the swine flu a pandemic. • It impacted approximately 74 countries and territories. By September of 2009, there were nearly 200,000 confirmed cases from over 100 countries and there were over 17,000 deaths (66). The pandemic was declared to be over by the WHO in 2010 	<p>It was found that the genes of the H1N1 virus are very similar to the genes of many influenza viruses that occur in pigs. H1N1 Swine Flu is believed to be passed from an animal, like a pig, to humans. Another mode of transmission is through human-to human contact (67). The transmission can occur through the following:</p> <ul style="list-style-type: none"> ○ Respiratory droplets that are produced when sneezing and coughing. ○ Infected patients contaminating inanimate objects or areas. ○ The virus can enter through the eyes, or the nose. 	<ol style="list-style-type: none"> 1. The H1N1 swine flu virus has a lower reproduction number, R0 value, than COVID-19. The 2009 swine flu virus had the reproduction number of 1.46 (68). <ul style="list-style-type: none"> ○ COVID-19 has a reproduction number in between 2-2.5. ○ This means that COVID-19 is more contagious than H1N1 and hence it can spread more easily. 2. Difference in Viral Load across age (68) The viral load in adults and children is found to be very similar this shows that the virus impacts all patients similarly as the amount of virus found is similar (69) <ul style="list-style-type: none"> ○ Studies suggest that H1N1, swine flu affects children more and the viral load is higher in children (70) ○ Asymptomatic patients with COVID-19 make detection and isolation harder³⁵. ○ H1N1, swine Flu, asymptomatic patients are very rare and this means that the patient can be diagnosed and isolated in the early stages preventing the virus from spreading further (71). 	<p>WHO recommendations (72):</p> <ul style="list-style-type: none"> • Washing hands regularly. • Maintaining a good respiratory hygiene which would include covering the mouth and nose when coughing and sneezing and using disposable tissues. • Self-isolation upon feeling unwell or feeling any of the symptoms. • Avoid touching the nose and the mouth. • Using proper protective gear when near sick patients. 	<p>[48], [66], [67], [68], [69], [70], [71], [72]</p>
<p>MERS</p>	<p>Jeddha, Saudi Arabia(28)</p>	<p>2012</p>	<ul style="list-style-type: none"> • The first outbreak of (Middle East Respiratory Syndrome) MERS occurred in 2012. The first patient that was diagnosed with MERS had a lower respiratory disease caused by the virus. • The countries that were majorly affected included the countries in Middle East. In total, 27 countries were affected by the Virus (73). 	<ul style="list-style-type: none"> • There is very little known about the MERS virus. It is a novel coronavirus that is believed to infect adults. The mortality rate of the patients infected with MERS virus was recorded to be 35%. • The transmission of the virus to humans is believed to have occurred from an animal. Many studies suggest that this spillover occurred from a camel (75). • There is very little known about the human-to-human transmission of the virus, as WHO has reported that most of the cases in Middle East have occurred through unprotected contact with infected animals like the camel. 	<p>1. There is still very little known about the MERS virus, with the information that is gathered it can be established that MERS-CoV did not spread as much Ebola due to these possible reasons:</p> <ol style="list-style-type: none"> 1. Transmission of the MERS virus from one person to another was found to be rare and it was only noted in people who were close to the infected patient like healthcare workers and family members. <ul style="list-style-type: none"> ○ The R0, reproduction number which determines how contagious a virus is, of MERS is reported to be less than 1. In a healthcare setting it has crossed (76). This means that if one 	<p>There are no vaccines or treatments that have been FDA approved for the prevention and treatment of MERS-Cov(28). WHO advises the following:</p> <ul style="list-style-type: none"> • Precaution while visiting places like the barn, farm, or any other places where camels and other animals are kept. • Ensuring that basic hygiene is kept in places where dromedary camels and other animals are kept. • Wash hands after touching the animals. 	<p>[73], [74], [75], [76], [77]</p>

		<ul style="list-style-type: none"> • Since the first outbreak there have been 2220 laboratory confirmed cases out of which 790 deaths occurred. • In 2015, there was a MERS outbreak in the Republic of Korea. It was the most impacted country outside of Middle East with the death of 36 people. The outbreak was linked to a traveler that travelled from the Middle East to The Republic of Korea (74). 	<p>Research also suggests that human-to-human transmission is really rare and in most cases the transmission has occurred in healthcare facility centers due to inadequate protection and prevention.</p>	<p>person is infected they are likely to infect less than one person.</p> <ul style="list-style-type: none"> ○ The R0 of COVID-19 is believed to be 2-2.5. This shows that COVID-19 is more contagious. <p>2. As MERS-CoV was less contagious than COVID-19 it was easier to contain and prevent its spread (77).</p> <ul style="list-style-type: none"> ○ By following the WHO guideline and restricting travel to the affected countries it was easier to contain MERS-CoV, especially as it was noted that the human to human transmission was rare. 	<ul style="list-style-type: none"> • Avoid consumption of uncooked and undercooked meat. Be precautions while consuming milk. • People who have are immunocompromised or have diabetes, renal failure, and chronic lung disease are considered to be highly compromised and they should practice extra precaution.
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Figures

FIGURE 1 PRISMA FLOW DIAGRAM

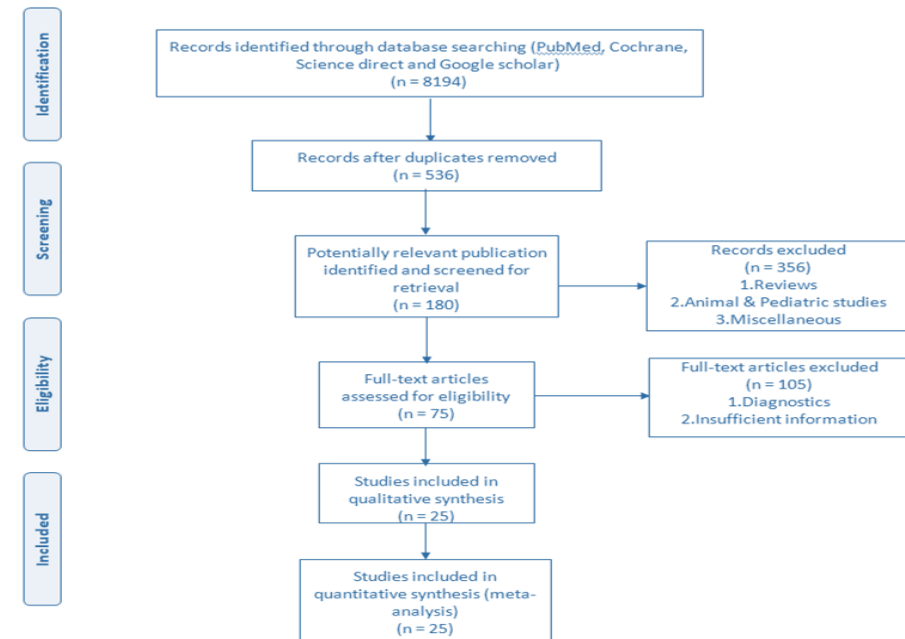


FIGURE 2 FOREST PLOT FOR AGE

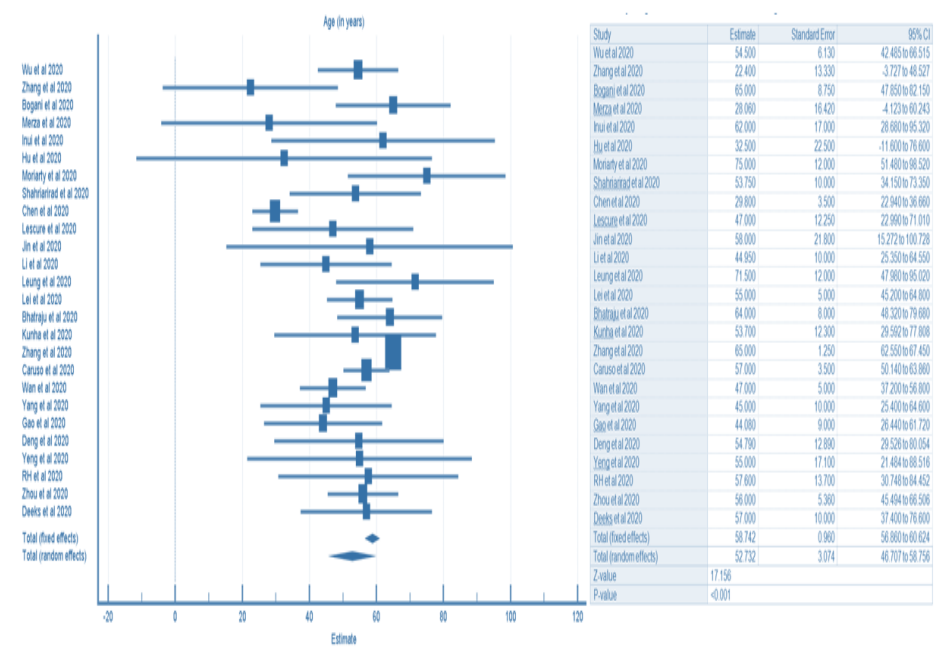
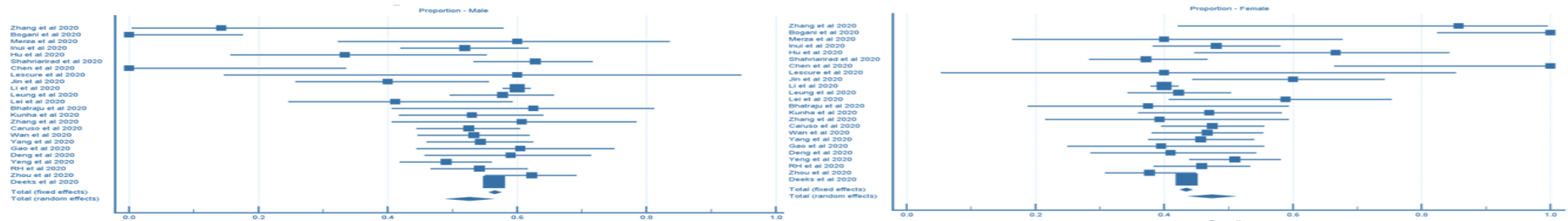


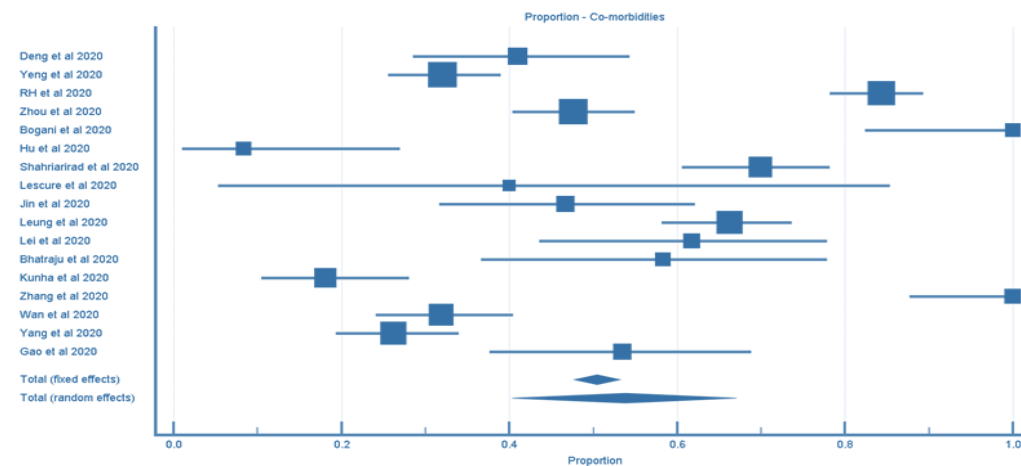
FIGURE 3 FOREST PLOT FOR GENDER



Study	Male	Proportion (%)	95% CI	Female	Proportion (%)	95% CI
Zhang et al 2020	1	14.286	0.361 to 0.57872	6	85.714	42.128 to 99.639
Bogani et al 2020	0	0.000	0.000 to 17.647	19	100.000	82.353 to 100.000
Mozza et al 2020	9	60.000	32.287 to 83.664	6	40.000	16.306 to 67.713
Inui et al 2020	54	51.923	41.908 to 61.826	50	48.077	38.174 to 58.092
Hu et al 2020	8	33.333	15.630 to 55.322	16	66.667	44.678 to 84.370
Shahriarirad et al 2020	71	62.932	53.237 to 71.737	42	37.068	28.263 to 46.763
Chen et al 2020	0	0.000	0.000 to 33.627	9	100.000	66.373 to 100.000
Lescure et al 2020	3	60.000	14.663 to 94.726	2	40.000	5.274 to 85.337
Jin et al 2020	18	40.000	25.698 to 55.669	27	60.000	44.331 to 74.302
Li et al 2020	1196	59.980	57.791 to 62.139	798	40.020	37.861 to 42.209
Leung et al 2020	89	57.792	49.580 to 65.698	65	42.208	34.302 to 50.420
Lei et al 2020	14	41.176	24.647 to 58.303	20	58.824	40.697 to 75.353
Bhatraju et al 2020	15	62.500	40.594 to 81.201	9	37.500	18.799 to 58.406
Kunha et al 2020	44	53.012	41.737 to 64.066	39	46.988	35.934 to 58.263
Zhang et al 2020	17	60.714	40.577 to 78.496	11	39.286	21.504 to 59.423
Caruso et al 2020	63	52.532	44.446 to 60.521	75	47.468	39.478 to 55.554
Wan et al 2020	72	53.333	44.555 to 61.962	63	46.667	38.038 to 55.445
Yang et al 2020	81	54.362	46.011 to 62.536	68	45.638	37.464 to 53.989
Gao et al 2020	26	60.465	44.410 to 75.023	17	39.535	24.977 to 55.590
Deng et al 2020	36	59.016	45.678 to 71.450	25	40.984	28.550 to 54.322
Yeng et al 2020	98	49.000	41.882 to 56.148	102	51.000	43.852 to 58.118
RH et al 2020	97	54.190	48.595 to 61.644	32	45.810	38.356 to 53.405
Zhou et al 2020	119	62.304	55.021 to 69.198	72	37.696	30.802 to 44.979
Deeks et al 2020	4656	56.395	55.318 to 57.469	3592	43.508	42.435 to 44.585
Total Count	8807	-	-	8215	-	-
Total (fixed effects)	12030	56.530	55.639 to 57.417	12030	43.404	42.517 to 44.294
Total (random effects)	12030	52.618	49.262 to 55.963	12030	47.372	44.028 to 50.727

Parameters	Test for heterogeneity		P-value for Test of Proportion
	Male	Female	
Q	104.8169	104.7388	<0.001
DF	23	23	
Significance level	P < 0.0001	P < 0.0001	
I ² (inconsistency)	78.06%	78.04%	
95% CI for I ²	67.83 to 85.03	67.80 to 85.02	

FIGURE 4 FOREST PLOT FOR CO-MORBIDITY



Study	Sample Size	Proportion (%)	95% CI
Deng et al 2020	61	40.984	28.550 to 54.322
Yeng et al 2020	200	32.000	25.596 to 38.947
RH et al 2020	179	84.358	78.192 to 89.347
Zhou et al 2020	191	47.644	40.385 to 54.977
Bogani et al 2020	19	100.000	82.353 to 100.000
Hu et al 2020	24	8.333	1.026 to 26.997
Shahriarirad et al 2020	113	69.912	60.568 to 78.181
Lescure et al 2020	5	40.000	5.274 to 85.337
Jin et al 2020	45	46.667	31.660 to 62.128
Leung et al 2020	154	66.234	58.182 to 73.648
Lei et al 2020	34	61.765	43.564 to 77.833
Bhatraju et al 2020	24	58.333	36.643 to 77.890
Kunha et al 2020	83	18.072	10.483 to 28.050
Zhang et al 2020	28	100.000	87.656 to 100.000
Wan et al 2020	135	31.852	24.103 to 40.417
Yang et al 2020	149	26.174	19.322 to 34.000
Gao et al 2020	43	53.488	37.655 to 68.824
Total (fixed effects)	1487	50.409	47.850 to 52.966
Total (random effects)	1487	53.780	41.059 to 66.257

Test for heterogeneity	
Q	377.2354
DF	16
Significance level	P < 0.0001
I ² (inconsistency)	95.76%
95% CI for I ²	94.37 to 96.80

FIGURE 5 FOREST PLOT FOR HYPERTENSION, DIABETES MELLITUS AND CORONARY HEART DISEASE

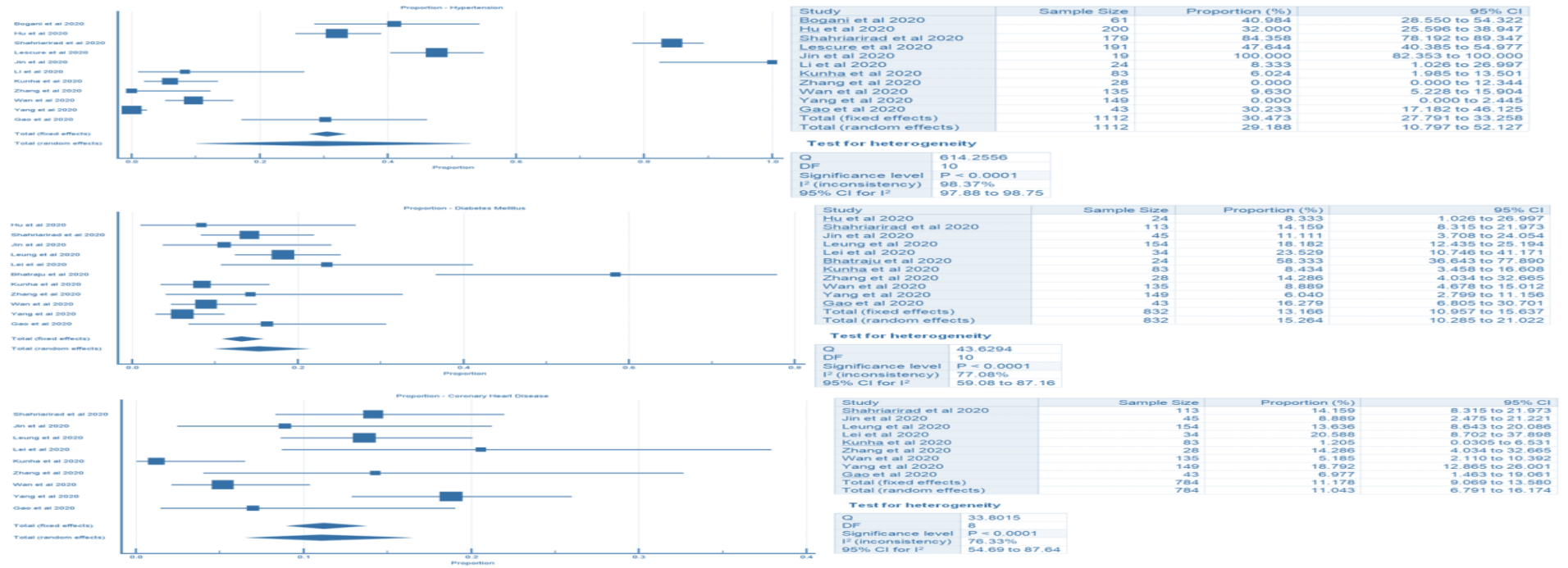


FIGURE 6 FOREST PLOT FOR PROPORTIONS OF ASYMPTOMATIC SUBJECTS

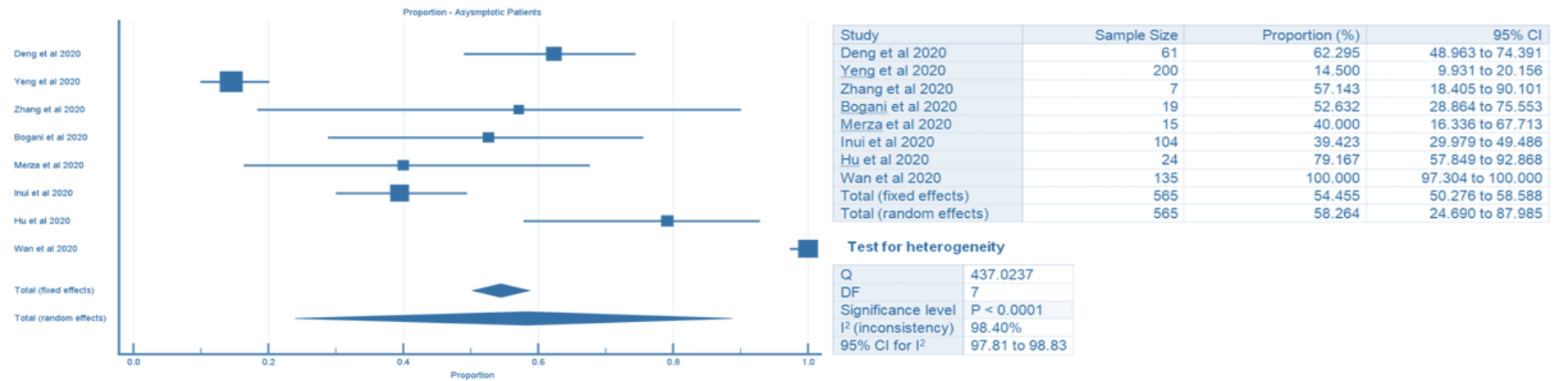
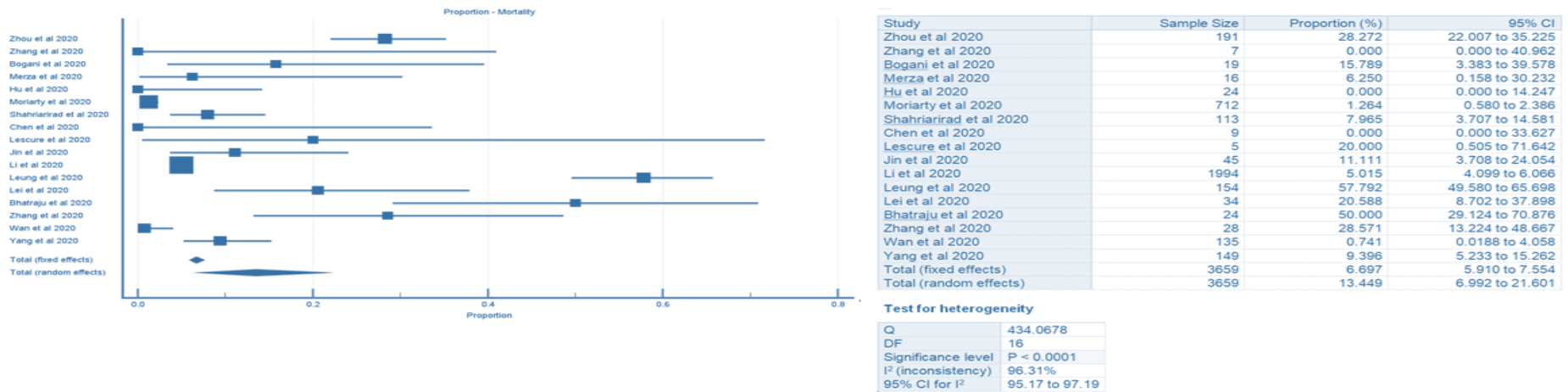


FIGURE 7 FOREST PLOT FOR PROPORTIONS OF MORTALITY PERCENTAGE



Funnel plot for assessing publication bias based on study proportions is shown in Figure 8. Circles indicate study point estimates. There was no clear asymmetry found and therefore, funnel plot demonstrates no significant publication bias

FIGURE 8 FUNNEL PLOT ASSESSING PUBLICATION BIAS

