Significance of comorbidities among COVID-19 patients as determinants of fatality in South Asia

This thesis is submitted to the Department of Mathematics and Natural Sciences, BRAC University, in partial fulfillment of the requirements for the degree of Master of Science in Biotechnology

By

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Declaration

It is hereby declared that:

1. The thesis presented is my own original work while completing my degree at BRAC University.

2. The thesis does not contain material previously published or written by a third party unless properly quoted by a complete and correct citation.

3. The thesis does not include material which has been accepted or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of assistance.

5. I would like to request the embargo of my thesis for 12M from the date of submission due to our attempt of publishing it in a reputed journal.

Student's Full Name & Signature:

Ashfia Nahreen

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Approval

The thesis/project titled "Comparative significance of comorbidities among COVID-19 patients as determinants of fatality in South Asia" submitted by Ashfia Nahreen (20376004) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Science in Biotechnology.

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Ethics Statement

The concept of this study was unique and thus did not have any conflict of interest. Moreover, the study did not use any animal model and in the case of human individuals, we took permission from the BRACU ethics committee.

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(Ashfia Nahreen)

Dedicated to:

All the families who have experienced the loss of a loved one

due to COVID-19 during this pandemic.

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List of Acronyms

ACE2: Angiotensin-Converting Enzyme 2

AKI: Acute Kidney Injury

ARDS: Acute Respiratory Distress Syndrome

BA: Bronchial Asthma

CFR: Case Fatality Rate

CKD: Chronic Kidney Diseases

CLD: Chronic Liver Diseases

COPD: Chronic Obstructive Pulmonary Diseases

COVID-19: Coronavirus Disease of 2019

CVA: Cerebrovascular Accidents

CVD: Cardiovascular Disease

DKA: Diabetes Ketoacidosis

DM: Diabetes

HRCT: High-Resolution Computed Tomography

HT: Hypertension

MI: Myocardial Infarction

NAAT: Nucleic Acid Augmentation Test

NSD: Nervous System Disorders

RAT: Rapid Antigen Test

RT-PCR: Reverse Transcription-Polymerase Chain Reaction

Abstract

Several comorbidities have been reported to be associated with SARS-CoV-2 related severity and mortality. However, there has been considerable variation in the prevalence estimates of these underlying conditions and their effects on COVID-19 morbidity and mortality in prior studies. This thesis aimed to review all published literature to determine these differences in the prevalence of comorbidities in South Asia. A search was conducted using PubMed, Scopus and Google Scholar to include all COVID-19 studies published between January 1st, 2020 to December 21st, 2022 reporting comorbidities with severity and mortality in three South Asian countries- namely, Bangladesh, India and Pakistan. Of 91 studies with 48908 participants, the most prevalent comorbidity among the overall population was diabetes (30.83%), hypertension (30.38%), cardiovascular diseases (9.75%) and chronic kidney diseases (8.06%). The presence of these comorbidities resulted in more COVID-19 severity and mortality, while presence of multiple comorbidities aggravated the condition even further. In patients with pre-existing diabetes and hypertension, a patient's condition deteriorated further when another comorbidity was present, mainly cardiovascular diseases and chronic kidney diseases. The study found that there were significant differences in the prevalence of comorbidities and the effect they had on disease severity and mortality across different geographical regions. In Bangladesh and India, the highest mortality was seen in diabetic patients infected with COVID-19 (61.23% and 49.25% respectively), whereas, in Pakistan, the highest mortality was seen in hypertensive patients infected with COVID-19 (63.69%). This study highlighted that the male gender, older age and comorbidities owned strong epidemiological evidence of associations with the severity and prognosis of COVID-19. Most frequent comorbidities reported in association with disease severity were diabetes, followed by hypertension and cardiovascular diseases. The data obtained from this study portrays the significant impact that the presence of pre-existing comorbidities had on the outcome of COVID-19 infection in Bangladesh, India and Pakistan. The study suggests that COVID-19 control strategies should be tailored according to comorbidities, age, and gender differences, and should take into account the specific geographical location to effectively stratify the risk and implement control measures. This study can also help to identify the gaps in the healthcare system and help to address the systemic issues that are leading to high mortality rates in these countries. From the public health perspective, this systematic review can help policymakers to better allocate resources and develop targeted interventions to improve the outcome of COVID-19 infection among these high-risk populations.

Keywords: COVID-19, comorbidity, Systematic review, South Asia, diabetes, hypertension

Introduction

In December of 2019, a virus, which was first seen in Wuhan City, China, began its tumultuous journey to result in a worldwide pandemic. The World Health Organization (WHO) on March 11, 2020, declared this novel coronavirus (COVID-19) outbreak a global pandemic. From then, there had been approximately 607 million cases of SARS-CoV-2 infection globally, along with 6.51 million deaths as of September 2022. [1] Among all the continents, Europe has suffered the most from the pandemic with 222 million cases, and the highest number of mortality of over 1.9 million. But among all the Asian countries, South Asia has had a comparatively lower count of cases. [1]

SARS-CoV-2, the virus that causes COVID-19, primarily enters the body through the ACE2 receptors found in the respiratory tract. Once inside, the virus uses its spike protein to bind to and enter host cells, where it can replicate and cause damage to the respiratory system. The infection is initially associated with the respiratory tract of infected individuals while the common symptoms of the disease include fever, cough, chest pain, lack of appetite, body aches, mild gastrointestinal diseases, myalgia and/or fatigue. Severe cases have also reported complications such as acute respiratory distress symptoms (ARDS), acute cardiac injury and secondary infection. [2] The host immune response is also a crucial aspect of the mechanism of COVID-19. Upon infection, the immune system mounts a response to clear the virus and repair the damage caused by the infection. However, in some cases, the immune response can be excessive and lead to what is known as a "cytokine storm," which can cause severe lung injury and other complications. Additionally, viral mutations, viral load, and individual's comorbidities also play a role in determining the severity of the disease.

Comorbidity, defined as the presence of one or more additional diseases or health conditions in addition to a primary disease, has been found to significantly increase the risk of severe illness and death from COVID-19. The mechanisms by which comorbidities increase susceptibility to COVID-19 are not fully understood, but it is thought that these conditions may weaken the immune system. Such patients were found to be more likely to experience higher complications and mortality [3]. Evidently, the presence of comorbid conditions such as diabetes, hypertension, cardiovascular ailments, chronic kidney and liver disease, malignancy, chronic respiratory disease and other communicable diseases in COVID-19 patients is connected to having greater disease severity [4]. This has significant implications for public health, as individuals with comorbidities make up a large portion of the population and are at increased risk of severe illness and death from COVID-19.

This study is imperative from a public health perspective. During the literature search, no study was found to report about the overall comorbid condition and its associated mortality. Most of the studies focused on particular disease conditions and its association with COVID-19 infected patients. Therefore, in our knowledge, this is the first study that reports about the number of comorbid conditions and the association with the mortality rate.

South Asia

This study has tried to evaluate the risk of severity and mortality in the outcome of COVID-19 patients by stratifying the comorbidity status in South Asia. Figure 1 shows the map of South Asia, which is the southern region of Asia, which is defined in both geographical and ethno-cultural terms. The region consists of the countries of Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Afghanistan and Sri Lanka. This study digs deep into the infectivity and mortality rates of 3 South Asian countries, namely Bangladesh, India and Pakistan. Three of the South Asian countries were not included in the literature search of the study - Afghanistan, Bhutan and Maldives. The government of Maldives acted quickly to control the situation by implementing public health measures as early as January 2020. Instead of imposing national lockdown and week-long restrictions, Maldives applied a strategy of gradual intensification of measures and localized restrictive measures and used multiple communication mechanisms to educate and engage the community [5]. All these factors proved effective in minimizing community spread and the local medical teams achieved a low Case Fatality Rate (CFR). Bhutan is a country with limited resources and a shortage of healthcare professionals, it's considered a lower-middle-income country. The country's approach to handling the COVID-19 pandemic is based on the principle of Gross National Happiness (GNH), which puts the well-being and happiness of its citizens above traditional economic indicators. The government implemented some unique and unconventional public health measures such as facility quarantine for those with high-risk exposure, an increase in quarantine period to 21 days, free testing and treatment, and population-based screening tests. Early and extensive contact tracing, extensive testing, effective communications, zoned travel restrictions, and adoption of physical distancing and hygiene measures limited COVID-19 transmissions within the country. All COVID-19 cases were treated in hospitals, and the country has had zero reported COVID-19 deaths [6]. Due to the success of these two countries in containing the virus, they have been excluded from this study. Additionally, Afghanistan has been facing political instability, social disruption and economic difficulties for decades, which might not allow for comprehensive data collection and analysis of the

COVID-19 pandemic. The country has been facing the challenges of lack of infrastructure and limited resources, which might not provide the data that is comparable to the other countries of SAARC. [7] Therefore, literature review search was conducted on Bangladesh, India, Pakistan, Nepal and Sri Lanka, but no studies published in Nepal and Sri Lanka met the eligibility criteria.

Figure 1: Map of South Asia

[Ref: Free World Maps. https://www.freeworldmaps.net/asia/southasia/political.html]

Review of literature

More than 1000 journal articles which were published in peer reviewed journals were reviewed in this section and those articles mainly reported the demographic characteristics, clinical profiles, symptomatology, etc. of COVID-19 patients. Additionally, articles published in World Health Organizations regarding comorbidity and COVID-19 and the global status of COVID-19 were also reviewed.

COVID-19 and Comorbidity

Comorbidities, age and gender have been identified as the strongest predictors of the prognosis of COVID-19 patients [8]. Systematic reviews and meta-analyses have confirmed that diabetes mellitus, hypertension and cardiovascular diseases are associated with the severity and mortality in COVID-19 patients. Moreover, other comorbidities vastly associated with COVID-19 severity are malignancy, chronic kidney diseases, chronic obstructive pulmonary diseases and chronic liver diseases. It is noteworthy that the presence of multiple comorbidities resulted in a more severe outcome for the COVID-19 patient [9]. A study conducted by Amin et al. [10] found that such patients had an increased hospitalization rate and longer recovery periods.

Figure 2 shows some of the chronic diseases and how SARS-CoV-2 affects the target organs, leading to complications such as ARDS, AKI, DKA, etc. One of the most severe complications of COVID-19 is Acute Respiratory Distress Syndrome (ARDS), which is a severe form of lung injury characterized by inflammation and fluid accumulation in the lungs. Individuals with comorbidities such as obesity and chronic obstructive pulmonary disease (COPD) are at increased risk of developing ARDS due to their already compromised respiratory function.

Diabetic patients are also at a higher risk of developing severe COVID-19, which may lead to Diabetic Ketoacidosis (DKA), a serious complication of diabetes characterized by high blood sugar levels and the presence of ketones in the blood. DKA can occur due to the stress of infection on the body, which can cause the body to release stress hormones that can raise blood sugar levels.

Acute kidney injury (AKI) and myocardial infarction are also complications that have been reported in COVID-19 patients, particularly in those with underlying comorbidities such as diabetes and hypertension. AKI can occur as a result of the body's inflammatory response to the virus, which can lead to damage to the kidneys. The virus can cause inflammation in the blood vessels leading to the heart, which can lead to clotting and obstruction of blood flow to the heart muscle, resulting in a heart attack.

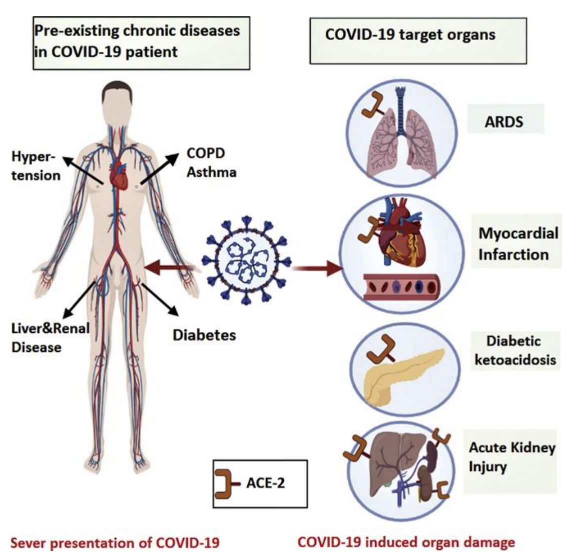

Figure 2: Diagram depicting the association between COVID-19 and chronic comorbidities

[Ref: Alyammahi, S. K. (2021). Diagram depicting the association between COVID-19 and chronic comorbidities. https://www.sciencedirect.com/science/article/pii/S1567134820304780]

COVID-19 in South Asia

Figure 3 shows the biweekly confirmed COVID-19 cases in India, Bangladesh and Pakistan. In India, the number of COVID-19 cases has been increasing at a rapid pace since the start of the pandemic, and India has the second highest number of confirmed cases in the world after the United States. [1] The country has been facing a second and third wave of the pandemic, with a significant increase in the number of cases and deaths reported in the middle of 2021 and early 2022. In Bangladesh, the number of confirmed cases has also been increasing rapidly, and the country has one of the highest rates of COVID-19 transmission in the region. In Bangladesh, there was a significant increase in the number of cases in the middle of 2021, following India. In Pakistan, the number of confirmed cases has also been increasing, and has reached a peak in the early months of 2022. The governments of these countries have implemented strict measures, such as lockdowns and travel restrictions, to curb the spread of the virus, but the number of cases continues to rise.

Figure 4 shows the biweekly confirmed COVID-19 deaths in the countries of interest. In India, the mortality rate has been relatively high, especially during the second and third wave of the pandemic. The country has reported one of the highest numbers of deaths in the world, with a high death rate per 100,000 people. Based on the available data, it appears that the mortality rate in India is relatively high compared to Bangladesh and Pakistan. During the second wave of the pandemic, the mortality rate in India, Bangladesh, and Pakistan has increased compared to the first wave. In all three countries, the overall trend is that the second wave has been more severe than the first and third one.

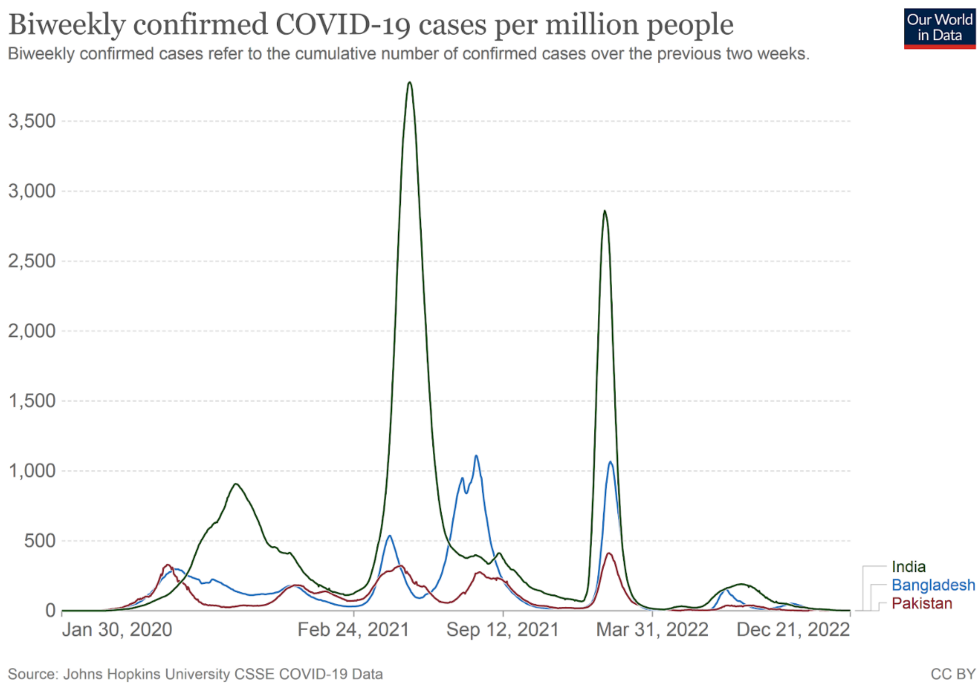

Figure 3: Biweekly confirmed COVID-19 cases per million people in Bangladesh, India and Pakistan between March 2020 to December 2022

[Ref: Our World in Data. https://ourworldindata.org/covid-deaths]

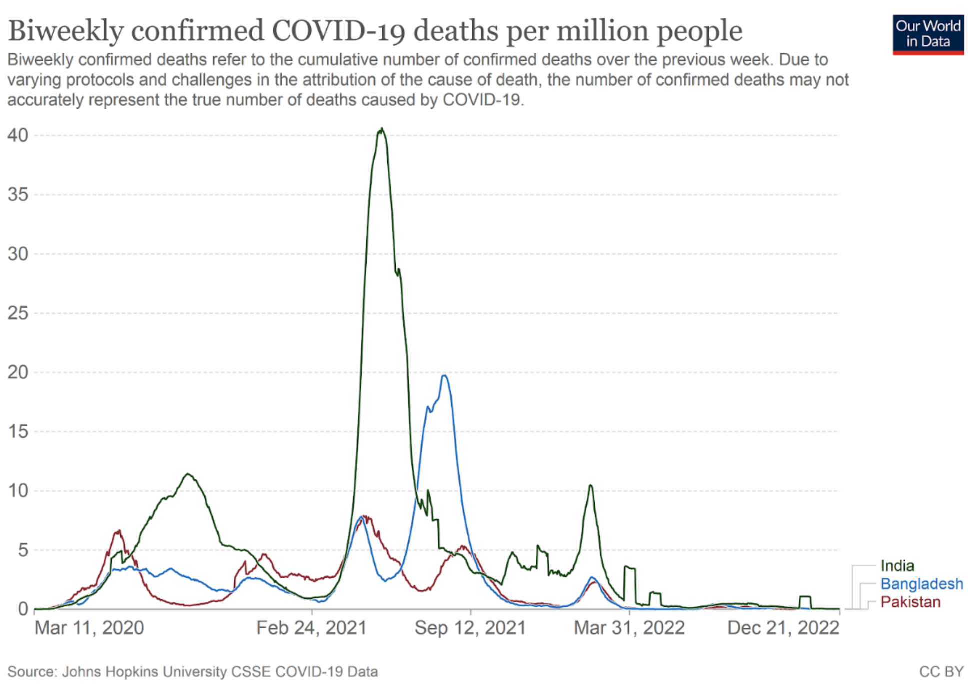

Figure 4: Biweekly confirmed COVID-19 deaths per million people in Bangladesh, India and Pakistan between March 2020 to December 2022

[Ref: Our World in Data. https://ourworldindata.org/covid-deaths]

Purpose of Study

In this age of post-pandemic medical research, it has never been more important to study the phenomenon of highly viral diseases and their effects on the health of the population with pre-existing non-communicable diseases. In this study, the purpose is to see the geographical variations in comorbid illnesses in the COVID-19 infected population of South Asia. This will help to shed some light on the mortality rates and patterns across the subcontinent to obtain a clearer picture of the mortality rates in this region to compare South Asia to the rest of the world. From the discussion in the literature review, it is clear that there is a significant knowledge gap among the scientific community to explain the behavior and outcomes of this novel virus. The correlation between comorbidity and COVID-19 has significant implications for public health and requires further research in order to effectively address the needs of individuals with comorbidities during the ongoing pandemic.

Objective

In this study, our primary objective was to see the prevalence of comorbidities among COVID-19 infected patients in South Asia by a systematic review of existing published literature. Secondly, it was to analyze the mortality rate of COVID-19 in the South Asian countries among the comorbid populations.

The scope of this study is to find the various comorbidities that have left a big impact on disease prognosis in South Asian countries. It has already been established that underlying disease conditions are strongly associated with increasing the mortality rate in COVID patients. However, throughout this literature review, no systematic review was found to focus on overall comorbid conditions in South Asian COVID-19 infected patients. Therefore, from the public health perspective, this systematic review can help policymakers while developing mitigation strategies against this kind of infectious disease in near future.

Methodology:

Guidelines and recommendations proposed by Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA 2020) were followed while conducting this study [11].

Search Strategy and Data Source:

An initial search was performed by one of the researchers (MHS) to identify the knowledge gap and define the study objective. Afterward, eligibility criteria were developed by following a thorough discussion between all the researchers. This study used two primary databases (SCOPUS and PubMed) and one search engine (Google scholar) as primary data sources. To identify relevant study articles per our eligibility criteria, the search was done independently (after logging out from all the google accounts) by one co-author (AN) between October 12, 2021, and December 21, 2022. Afterward, another co-author (BB) cross-checked the overall procedure and updated the existing literature from January 1, 2023, to January 25, 2023. The search strategy was designed to retrieve all articles published between January 2020 to January 2023 regarding comorbidities and associated outcomes related to COVID-19 patients in South Asia. Various combinations of Boolean operators' keywords used in the search included: 'COVID-19', 'SARS-CoV-2', 'comorbidity,' 'diabetes,' 'hypertension,' 'heart disease,' 'cancer,' 'kidney disease,' 'liver disease,' 'South Asia,' 'Bangladesh,' 'India,' 'Pakistan', 'Nepal' and 'Sri Lanka.' The position of the keywords was rearranged in the search bar to cover all relevant articles for this study. In addition, forward and backward search was conducted by manually checking the citing and reference lists of the individual articles, respectively.

Furthermore, to maximize search efficiency, corresponding authors profiles (ResearchGate, ORCID, and Google Scholar) and 'similar articles' suggested by the repositories (PubMed, SCOPUS, and Google Scholar) were also explored. Moreover, we also examined the database of the World Health Organization (WHO), Covid-19 Primer (a database that reported every 24hrs about the scientific progress in to fight against COVID-19), and Johns Hopkins Coronavirus Resource Center as an additional source for country-specific COVID-19 Information following our eligibility criteria. The Medical subject heading (MeSH) terms and text used for the literature search are given in Table 1.

Eligibility Criteria:

In this study, to identify reported comorbidity associated with COVID patients, we followed the list of underlying disease conditions provided by the Center for Disease Control and Prevention (CDC) and the International Classification of Diseases 10th edition (ICD-10) [12, 13].

Articles were included in this systematic review if they met these criteria:

1. Articles highlighting the comorbid conditions of COVID-infected patients and COVID-death patients.
2. Peer-reviewed original articles focused on COVID patients in South Asian countries (India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan, Maldives, and Afghanistan).
3. Studies measure the presence of COVID-19 on participants via RT-PCR.
4. All kinds of original studies, irrespective of their study design, such as retrospective, prospective, cross-sectional, case-control, randomized control trials, and others, were included in this review if they satisfy our eligibility criteria.

Moreover, the following exclusion criteria were also applied:

1. Studies focused on countries located outside South Asia.
2. Non-peer-reviewed publications, letters to the editor, short communications, review articles, meta-analyses, etc.
3. Studies that reported the testing procedure for COVID-19 other than RT-PCR.
4. Studies that met our inclusion criteria, but the sample size is too small (< 15 participants).
5. Studies that satisfied the inclusion criteria but full-text journals could not be obtained from the authors after requesting it

Mendeley reference manager (version 2.62.0) had been used for reference management and to remove duplication. After eliminating duplicates, titles, and abstracts were screened, full-text screening was implemented for the relevant articles. Studies were excluded if the inclusion criteria were not fulfilled, and any discrepancies regarding study selection were resolved through group discussions between all the co-authors.

Data extraction:

As per the eligibility criteria, data extraction was performed by AN and BB between February 1, 2023, to February 23, 2023. Afterward, two other researchers from the group (MHS and NSD) cross-checked the overall procedure to finalize the total number of eligible articles. Any discrepancies during data extraction were resolved through group discussion.

An excel sheet was used to develop a summary table that represents characteristics of our selected study articles. The summary table contain the following Information's; References (author and year of publication), study location, the total number of COVID patients, number of participants with comorbidities, age, method of measurement, number of participants who had succumbed to the disease as well as their respective comorbidities, and the key Information relating the two factors - comorbidity and COVID-19. Data regarding the mortality and infectivity of COVID-19 in comorbid patients had been arranged in separate tables based on countries and specific comorbidities.

Evaluation of study quality for selected articles:

Two authors (AN and BB) independently assessed the methodological quality of our selected study articles by following the 9-item tool developed specifically for systematic review prevalence data [14, 15]. Based on the critical appraisal tool scoring system, "1" was implied for "Yes" and "0" for "NO or Unclear." Studies total scores ranged between 0-5 is designated as a high risk of bias, 6-7 as a moderate risk of bias, and 8-9 as a high risk of bias. The risk of bias was assessed for all included articles. Any disagreements during the assessment were resolved through discussion with other members of the group.

Statistical Analysis:

Number of COVID affected patients and COVID death patients, COVID patients with specific comorbidities like diabetes, hypertension, heart disease, and others were considered as summary measurement. Microsoft excel version 16 was used for descriptive statistical analysis (frequency). Forest plot was created for mostly reported three comorbidities by using a statistical software named MedCalc. Since the individual studies included in our final summary table did not report the effects of all these variables, we used the random-effect model to obtain pooled prevalence with a 95% confidence interval.

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(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (diabetes) AND TITLE-ABS-KEY (sri AND lanka)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (bangladesh)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (india)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (nepal)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (pakistan)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (south AND asia)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (covid-19) AND TITLE-ABS-KEY (hypertension) AND TITLE-ABS-KEY (sri AND lanka)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (bangladesh)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (india)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (nepal)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (pakistan)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (south AND asia)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (sars-cov-2) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (sri AND lanka)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (bangladesh)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (india)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (nepal)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (pakistan)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (south AND asia)) AND PUBYEAR > 2019 AND PUBYEAR > 2019
(TITLE-ABS-KEY (coronavirus AND disease) AND TITLE-ABS-KEY (comorbidity) AND TITLE-ABS-KEY (sri AND lanka)) AND PUBYEAR > 2019 AND PUBYEAR > 2019

Table 1: Search strategy for literature search

Results

Figure 5 shows the search pattern and exclusion of articles with specific reasons at each step. A total of 5039 study articles were retrieved from three databases by using the search strategy given in Table 1. Among these studies, 4948 articles were excluded as they were unable to fully fit in the inclusion criteria. Finally, 91 study articles were selected for the review. Out of 91 eligible studies, 64 were conducted in India, 17 in Pakistan and 10 in Bangladesh.

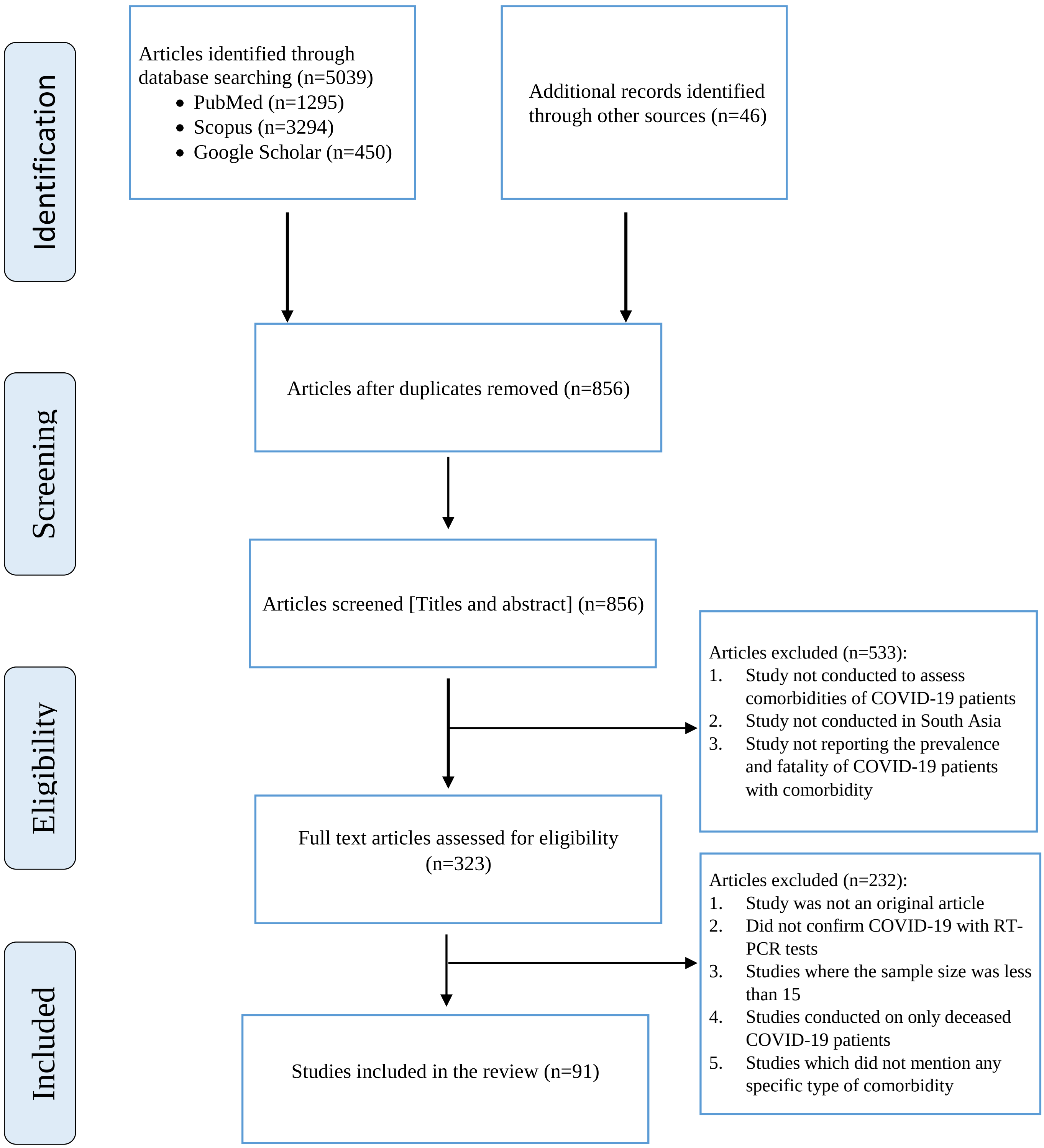

Figure 5: PRISMA chart showing the summary of search result and selection of studies for final analysis

Characteristics of selected study articles

Table 2 shows the characteristics and summary of the selected studies. Table 2a shows the characteristics of the selected studies, such as the total population, location of the conducted study, genders of the population, method of COVID-19 detection, etc. Table 2b shows the reported comorbidities of the overall population - both survivors and non-survivors. Table 2c shows the reported comorbidities in the deceased population.

Prevalence of comorbidities among both the survived and non-survived population was mentioned in all studies. Most of the studies detected the presence of COVID-19 using RT-PCR, however, some studies utilized other methods such as NAAT (Nucleic Acid Amplification Test), RAT (Rapid Antigen Test), HRCT (High-resolution computed tomography) and radiography in conjunction to RT-PCR.

Out of the 91 studies, 86 studies were hospital-based; it was either a single center or multicenter study. A retrospective study looks back in time to examine past events, such as past medical history or previous treatment outcomes and there were 54 retrospective studies among the selected studies. A prospective study looks forward in time to examine future events, such as the development of a disease or the effectiveness of a new treatment and 9 prospective studies were included in this review. An observational study examines the behavior of a population or group of people without manipulating or interfering with the subjects; among the selected studies, there were 21 observational studies. There was only one randomized controlled trial, in which subjects are randomly assigned to different groups, one of which receives a specific intervention (e.g., a drug or treatment) while the other group serves as a control. For the purpose of the study, only the population which did not get any specific interventions was included. There were 2 hospital based case series and 2 hospital based case control studies - where a population without any comorbidities was compared to a comorbid population. There were 8 cross-sectional studies, which examined a group of people at a specific point in time to determine the prevalence of a disease or other health condition. Lastly, there were 11 cohort studies included in this review. A cohort study follows a group of individuals over time to determine the incidence of a particular disease or condition and to identify potential risk factors for the disease.

The summary table in Table 2b and 2c noted 11 comorbidities among the COVID-19 population - diabetes, hypertension, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary diseases, chronic liver diseases, cancer, hypo/hyperthyroidism, obesity, nervous system disorders and cerebrovascular accidents. A comorbidity was included in the summary table if they were reported in more than 10 studies and they were selected for further analysis if they appeared in more than 30 studies. Thus, obesity, hypo/hyperthyroidism and nervous system disorders were excluded from in-depth analysis.

To show the complete picture of comorbid conditions among the COVID-19 patients, the overall findings were segregated into three sections - studies where the sample population was below 14 years of age (Table 3), studies conducted explicitly on COVID-19 patients (Table 4) and studies conducted on COVID-19 infected patients with a pre-existing comorbidity (Table 5).

SL #	References	Study Location	Study Design	Method	Number of participants	Gender		Number of deceased participants	Gender	
						M	F		M	F
1	Padmaprakash et al, 2021	Northern India	hospital-based cohort study	RT-PCR	1536	1357	179	76	59	17
2	Saha et al, 2021	Chittagong - Bangladesh	hospital-based retrospective study	RT-PCR	168	134	34	95	75	20
3	Islam et al, 2020	Dhaka - Bangladesh	Retrospective Cohort study	RT-PCR	1016	651	365	25	19	6
4	Mowla et al, 2020	Dhaka - Bangladesh	Retrospective - cross sectional study	RT-PCR	100	63	37	10	10	0
5	Hossain et al, 2021	Dhaka - Bangladesh	hospital based cross sectional study	RT-PCR/HRCT	486	306	180	94	66	28
6	Soni et al, 2021	Chandigarh - India	hospital based study	RT-PCR	114	66	48	3	Not mentioned	
7	Bobdey et al, 2021	Maharastra - India	hospital based-retrospective study	RT-PCR	1233	984	249	72	50	22
8	Mehta et al, 2021	Delhi - India	hospital based retrospe	RT-PCR	186	105	81	27	16	11

			ctive cohort study							
9	Gupta et al, 2020	New Delhi - India	hospital based prospective - study	RT-PCR	200	116	84	19	Not mentioned	
10	Sharma et al, 2021	New Delhi - India	hospital based retrospective chart review	RT-PCR/CBNAAT	100	59	41	27	16	11
11	Malik et al, 2020	Dhaka - Bangladesh	hospital based - cross sectional study	RT-PCR	139	57	82	1	Not mentioned	
12	Vadiraj et al, 2022	New Delhi - India	hospital based retrospective cohort study	RT-PCR	708	561	147	96	Not mentioned	
13	Jat et al, 2021	India	hospital based retrospective	RT-PCR / CBNAAT	402	247	155	13	Not mentioned	
14	Sarkar et al, 2022	Eastern India	hospital based - descriptive study	RT-PCR	128			3	Not mentioned	
15	Akhtar et al, 2021	Rawalpindi-Islamabad, Pakistan	Retrospective observational study	PCR	1812	1253	559	469	313	156
16	Nasir et al, 2021	Karachi - Pakistan	hospital based observational study	RT-PCR	445	298	147	58	47	11
17	Ayaz et al, 2020	Karachi - Pakistan	hospital based retrospective cohort study	RT-PCR	66	40	26	9	9	0
18	Ch et al, 2020	Lahore - Pakistan	hospital based cross	RT-PCR	42	19	23	3	Not mentioned	

			sectional study							
19	Haq et al, 2020	Khyber Pakhtunkhwa - Pakistan	hospital based retrospective cohort study	RT-PCR	179	150	29	52	38	14
20	Jayaswal et al, 2021	New Delhi - India	hospital based retrospective case control study	RT-PCR/RAT	813	559	254	52	Not mentioned	
21	Gupte et al, 2022	Various states - India	hospital based-retrospective	RT-PCR	2329	1570	583	134	108	26
22	Mammen et al, 2021	India	Randomized Controlled Trial	RT-PCR	451	346	105	65	52	13
23	Mathew et al, 2021	Bengaluru - India	hospital based - retrospective	RT - PCR	62	48	14	13	10	3
24	Chandrasekaran et al, 2021	Chennai - India	hospital based retrospective cohort study	RT - PCR and CT	102	73	29	33	24	9
25	Sindhu et al, 2021	South India	hospital based retrospective	PCR	190	155	35	42	35	7
26	Kunal et al, 2020	India - Rajasthan	hospital based - retrospective	RT - PCR	108	70	38	30	19	11
27	Sharif et al, 2021	Bangladesh - clinics from eight division	hospital based - retrospective	RT-PCR	799	526	273	318	Not mentioned	
28	Kute et al, 2021	Ahmedabad - India	hospital based - Retrospective	RT-PCR	157	133	24	15	14	1
29	Gupta et al, 2021	Kolkata - India	hospital based -	RT - PCR	710	530	180	50	Not mentioned	

			prospective							
30	Sinha et al, 2021	Mumbai - India	hospital based - prospective	RT - PCR	131	75	56	27	17	10
31	Gopalan et al, 2022	Tamil Nadu - India	hospital based - retrospective study	RT-PCR	746	466	280	259	173	86
32	Rehman et al, 2021	Islamabad - Pakistan	hospital based - retrospective	RT-PCR	2048	1217	831	590	415	175
33	Kazmi et al, 2021	Karachi - Pakistan	hospital based - retrospective study	RT-PCR	43	25	18	11	8	3
34	Ejaz et al, 2021	Karachi - Pakistan	hospital based - Retrospective	RT-PCR	71	62	9	41	Not mentioned	
35	Prasad et al, 2021	India	hospital based prospective - study	RT-PCR	263	173	90	35	27	8
36	Baqi et al, 2021	Karachi - Pakistan	hospital based - observational study	PCR	252	188	64	95	68	27
37	Asghar et al, 2021	Lahore and Peshawar - Pakistan	hospital based - retrospective cohort study	PCR	70	38	32	30	19	11
38	Chachar et al, 2021	Lahore - Pakistan	hospital based - retrospective study	PCR	428	291	154	37	23	14
39	Karthi et al, 2021	Chandigarh - India	hospital based - retrospective study	RT PCR	31	16	15	1	Not mentioned	
40	Muttineni et al, 2021	Hyderabad, India.	hospital based	RT-PCR	109	78	31	52	41	11

41	Hussain et al, 2020	Karachi - Pakistan	hospital based descriptive case series	RT-PCR	266	238	28	18	Not mentioned	
42	Khalid et al, 2021	Punjab - Pakistan	hospital based retrospective study	RT-PCR	317	198	111	57	Not mentioned	
43	Lamech et al, 2021	Chennai - India	hospital based prospective study	RT-PCR	183	118	65	24	Not mentioned	
44	Meshram et al, 2021	India	hospital based - retrospective cohort study	RT-PCR	61	54	7	16	15	1
45	Pednekar et al, 2022	Maharashtra - India	hospital based - retrospective study	Antigen test/RT-PCR/CBNAAT	231	150	81	92	56	36
46	Bhinder et al, 2021	Delhi - India	hospital based - retrospective study	RT-PCR	213	132	81	52	33	19
47	Pranshu et al, 2022	Rajasthan - India	hospital based retrospective	RT-PCR	65	41	24	12	10	2
48	Jamir et al, 2021	Andhra Pradesh - India	hospital based retrospective	RT-PCR	266	259	7	101	98	3
49	Asghar et al, 2022	Lahore - Pakistan	hospital based retrospective	RT-PCR	43	26	17	15	9	6
50	Roy et al, 2021	New Delhi - India	hospital based retrospective observational study	RT-PCR/CB-NAAT	141	80	61	54	32	22
51	Singh et al, 2021	Bihar - India	hospital based cross-	RT-PCR	156	118	38	18	16	2

			sectional study							
52	Anand et al, 2022	Kerala - India	hospital based retrospective study	RT-PCR	476	265	211	30	20	10
53	Asaduzzaman et al, 2022	Sylhet - Bangladesh	hospital based retrospective study	RT-PCR	245	158	87	43	26	17
54	Parvin et al, 2022	Dhaka - Bangladesh	hospital based cross-sectional study	RT-PCR	972	624	348	161	127	34
55	Rana et al, 2022	Delhi - India	hospital based retrospective study	RT-PCR	2586	1800	786	317	Not mentioned	
56	Parhad et al, 2022	Raipur - India	hospital based retrospective study	RT-PCR/RAT/TrueNAT	5552	3557	1995	559	430	129
57	Dravid et al, 2022	Pune - India	hospital based retrospective study	RT-PCR/RAT	59	47	12	15	11	4
58	Kantroo et al, 2021	Delhi - India	hospital based retrospective study	RT-PCR	1192	832	360	73	55	18
59	Prakash et al, 2020	Uttar Pradesh - India	hospital based retrospective observational study	PCR	17	15	2	1	1	0
60	Akhtar et al, 2021	Islamabad - Pakistan	hospital based retrospective study	PCR	659	452	207	469	313	156
61	Alam et al, 2022	Karachi - Pakistan	hospital based retrospe	RT-PCR	209	149	60	60	42	18

			ctive study							
62	Asaduzzaman et al, 2022	Sylhet - Bangladesh	hospital based retrospective study	PCR/radiography	442	291	151	55	34	21
63	Vardhan et al, 2021	Patna - India	hospital based retrospective observational study	RT-PCR	261	195	66	172	Not mentioned	
64	Rai et al, 2021	Patna - India	hospital based retrospective observational study	RT-PCR/RAT	984	762	222	254	203	51
65	Zirpe et al, 2021	Pune - India	hospital based retrospective observational study	RT-PCR	84	70	14	13	13	0
66	Mittal et al, 2022	Panjab - India	hospital based retrospective observational study	RT-PCR	4559	3005	1554	967	Not mentioned	
67	Thakare et al, 2022	Mumbai - India	hospital based observational study	RT-PCR	234	152	82	76	54	22
68	Yadla et al, 2021	Hyderabad - India	hospital based observational study	RT-PCR	84	57	27	36	23	13
69	Desai et al, 2021	Ahmedabad - India	hospital based retrospective observational study	RT-PCR	112	80	32	15	10	5

70	Nigam et al, 2021	Patna - India	hospital based descriptive study	RT-PCR	252	179	73	46	37	9
71	Kayina et al, 2020	Delhi - India	hospital based prospective observational study	RT-PCR	235	160	85	20	14	6
72	Banerjee et al, 2021	Gujarat - India	hospital based retrospective study	RT-PCR	58	32	26	22	Not mentioned	
73	Choudhary et al, 2022	India	hospital based retrospective study	RT-PCR	218	169	49	30	23	7
74	Haroon et al, 2022	Karachi - Pakistan	hospital based retrospective study	RT-PCR	102	58	44	38	22	16
75	Chowdhury et al, 2022	Chittagong - Bangladesh	clinical trial study	RT-PCR	208	155	53	57	38	19
76	Chopra et al, 2022	Kolkata - India	hospital based retrospective observational cross-sectional study	RT-PCR	83	45	38	36	21	15
77	Bansode et al, 2022	Maharashtra - India	hospital based prospective observational study	RT-PCR	111	75	36	58	36	22
78	Budhiraja et al, 2021	Delhi - India	multicenter retrospective observational case	RT-PCR	361	361	261	100	73	47

			control study							
79	Ramaswamy et al, 2020	Mumbai - India	hospital based observational study	RT-PCR	230	124	106	23	10	13
80	Elavarasi et al, 2021	Jhajjar-India	hospital based retrospective study	RT-PCR/NAAT/RAT	2017	1320	697	406	274	132
81	Kute et al, 2020	India	multicenter cohort study	RT-PCR	250	215	35	29	26	3
82	Mohan et al, 2020	India	hospital based prospective study	RT-PCR	144	134	10	2	2	0
83	de Souza et al, 2020	Mumbai - India	hospital based observational study	RT-PCR	689	338	351	156	94	62
84	Havaldar et al, 2022	India	multicenter cohort study	RT-PCR	174	121	53	76	56	20
85	Parry et al, 2020	Kashmir - India	hospital based prospective observational study	RT-PCR	147	104	43	2	Not mentioned	
86	Mohandas et al, 2021	Tamil Nadu - India	hospital based retrospective study	RT-PCR/Radiography	3345	2314	1031	142	111	31
87	Shankar et al, 2021	South India	hospital based cross-sectional observational study	RT-PCR	90	60	30	31	20	11
88	Rao et al, 2021	India	hospital based retrospe	RT-PCR	123	71	52	14	Not mentioned	

			ctive study							
89	Mahapatra et al, 2022	India	hospital based case series	RT-PCR	44	20	24	17	Not mentioned	
90	Bhandari et al, 2021	India	hospital based observational study	RT-PCR	20	17	3	5	4	1
91	Dosi et al, 2020	Madhya Pradesh - India	hospital based retrospective study	RT-PCR	365	212	153	31	21	10

Table 2a: Characteristics of the selected study articles

SL #	References	Reported comorbidities on COVID patients										
		DM	HT	CVD	CKD	CLD	CVA	COPD/BA	Cancer	Obesity	Thyroid	NSD
1	Padmaprakash et al, 2021	103	130	49	15	3	11	8	45			
2	Saha et al, 2021	88	69	28	5			15				
3	Islam et al, 2020	179	145	40	21	13		85	9			
4	Mowla et al, 2020	16	21	8	8	3	1	6	2	5		
5	Hossain et al, 2021	192	201	37	20	6		53	12			
6	Soni et al, 2021	17	19	2	3	1	1	2		1		
7	Bobdey et al, 2021	45	53									
8	Mehta et al, 2021	34	45	11				2	186		30	
9	Gupta et al, 2020	32	46	9	4		5	1	5		6	
10	Sharma et al, 2021								13			
11	Malik et al, 2020	10	21	6				10				
12	Vadiraj et al, 2022	130	126	54	13		6	19	36			

13	Jat et al, 2021			24	13			7	36			10
14	Sarkar et al, 2022			4					2			3
15	Akhtar et al, 2021	532	625	243	93			111	13			30
16	Nasir et al, 2021	162	167	74	31	8	10		22			
17	Ayaz et al, 2020	25	30	10	3			2	4			
18	Ch et al, 2020	1		2	7	1			2			1
19	Haq et al, 2020	48	62	29	3		2	27				
20	Jayaswal et al, 2021	236	223									
21	Gupte et al, 2022	679	465	145				100				
22	Mammen et al, 2021	196	169	31	17		4	15		31		
23	Mathew et al, 2021	34	38	5								
24	Chandrasekaran et al, 2021		53	10	10	10	8			27		
25	Sindhu et al, 2021	137	127	57	43		10					
26	Kunal et al, 2020	35	41	14	9			14	3			
27	Sharif et al, 2021	261		337	78			104	30	144		
28	Kute et al, 2021	38	114	17	157					38		
29	Gupta et al, 2021	53	87	49	39			21	50			37
30	Sinha et al, 2021	38	99	29				11			6	
31	Gopalan et al, 2022	299	219	75	72	8		35	10	10		
32	Rehman et al, 2021	608	975	1177	68	79	629	289	50			
33	Kazmi et al, 2021	14	35	12								
34	Ejaz et al, 2021	39	39	24	9							
35	Prasad et al, 2021	142			263							

36	Baqi et al, 2021	132	128	37						22		
37	Asghar et al, 2021	9	14	3	7	3		8				
38	Chachar et al, 2021	168	195	61	29			54	9	51		
39	Karthi et al, 2021			2	1							3
40	Muttineni et al, 2021	37	34	10	8			5			5	
41	Hussain et al, 2020	36	48	24	2			8	2			
42	Khalid et al, 2021	112	124	28		40		13				
43	Lamech et al, 2021	62	140	45	118			11				
44	Meshram et al, 2021	15	19		61							
45	Pednekar et al, 2022	141	179	24	4	12	8	12		82	10	
46	Bhinder et al, 2021	75	177	19	213	2		4			11	
47	Pranshu et al, 2022	21	21	4	2			2			5	
48	Jamir et al, 2021	100	77					14		200		
49	Asghar et al, 2022	43	11	3	3	1		2	43			
50	Roy et al, 2021	53	58	7	8			2			18	
51	Singh et al, 2021	17	16									
52	Anand et al, 2022	214	209	60	17			36	9		56	
53	Asaduzzaman et al, 2022	175	195	75	56		18	32				
54	Parvin et al, 2022	410	424	76	46	14		109	22			
55	Rana et al, 2022	1002	903		170							
56	Parhad et al, 2022	1410	1649	322	241	53		81	87	17	299	61

57	Dravid et al, 2022	53	24	7	9	2	1			2	3	
58	Kantroo et al, 2021	319	335	78	96		17	31	46			
59	Prakash et al, 2020	5	2	1				1				
60	Akhtar et al, 2021	331	377	163	57			74	8			20
61	Alam et al, 2022	84	105	27	25	12		23				
62	Asaduzzaman et al, 2022	281	311	98	78		20	54				
63	Vardhan et al, 2021	187	222	60	261			21				
64	Rai et al, 2021	330	306	57	53			37	18		93	
65	Zirpe et al, 2021	54	31	4	3							
66	Mittal et al, 2022	2090	1079	268	215	69		19				
67	Thakare et al, 2022	96	180	20	199		16					
68	Yadla et al, 2021	45	79	7	84		2	1				
69	Desai et al, 2021	19	37	13	6			13	4			9
70	Nigam et al, 2021	86	98	20	17	9		15	6			
71	Kayina et al, 2020	54	65	13	22	10		5	26			
72	Banerjee et al, 2021	11	38	9	58							
73	Choudhary et al, 2022	56	200		218							
74	Haroon et al, 2022	57	58	28				9				
75	Chowdhury et al, 2022	28	38	15	2		3	12	1		4	
76	Chopra et al, 2022	23	26	5				8		19		
77	Bansode et al, 2022	71	72	19	25		6	5				

78	Budhiraja et al, 2021	66	157	51							33	
79	Ramaswamy et al, 2020	30	25	2					230			
80	Elavarasi et al, 2021	437	457	96	25	5		54	102		86	29
81	Kute et al, 2020	80	210	30	250							
82	Mohan et al, 2020	16	3	1				3			3	1
83	de Souza et al, 2020	67	66	17	20	2		11	10			
84	Havaldar et al, 2022	70	62	18	10	5	3	11	4			
85	Parry et al, 2020	5	9			1						
86	Mohandas et al, 2021	1240	974	200	52			105			94	
87	Shankar et al, 2021	31	1		90							
88	Rao et al, 2021			7	5				3			
89	Mahapatra et al, 2022	10	37	7	44							
90	Bhandari et al, 2021	11	19	3	20							
91	Dosi et al, 2020	82	92	14	9			13	2	5	11	

Table 2b: Reported comorbidities of the overall population of the selected study articles

SL #	**References**	**Reported comorbidities on deceased COVID patients**										
		DM	**HT**	**CVD**	**CKD**	**CLD**	**CVA**	**COPD/ BA**	**Cancer**	**Obesity**	**Thyroid**	**NSD**
1	Padmaprakash et al, 2021	23	28	11	4	2		2	11			
2	Saha et al, 2021	53	41	23	3			3				
3	Islam et al, 2020	9	9	4	4	3		10	2			

4	Mowla et al, 2020	4	5	4	4			2	1			
5	Hossain et al, 2021	44	49	11	8	3		9	4			
6	Soni et al, 2021	3			2							
7	Bobdey et al, 2021	34	32									
8	Mehta et al, 2021	10	9	4					27		4	
9	Gupta et al, 2020	8	8	1					1			
10	Sharma et al, 2021								2			
11	Malik et al, 2020			1								
12	Vadiraj et al, 2022	34	31	15	2		3	5	12			
13	Jat et al, 2021			5	1				1			5
14	Sarkar et al, 2022			1					1			1
15	Akhtar et al, 2021	245	294	135	56			69	9			21
16	Nasir et al, 2021	28	31	20	12				7			
17	Ayaz et al, 2020	8	8	6	3				2			
18	Ch et al, 2020				1	1			1			
19	Haq et al, 2020	24	31	19	2		2	13				
20	Jayaswal et al, 2021	29	17									
21	Gupte et al, 2022	62	23	19				10				
22	Mammen et al, 2021	32	30	8	6		1	5		6		
23	Mathew et al, 2021	10	11	2								
24	Chandrasekaran et al, 2021		19	6	5	6	3			10		
25	Sindhu et al, 2021	35	31	19	10		3					
26	Kunal et al, 2020	14	17	5								
27	Sharif et al, 2021	237		288								
28	Kute et al, 2021	5	10	3	15					8		

29	Gupta et al, 2021	16	21	5	11			5	5			10
30	Sinha et al, 2021	15	22	9				3				
31	Gopalan et al, 2022	145	106	42	50	7		11	8	8		
32	Rehman et al, 2021	395	444	202	20	41	310	143	21			
33	Kazmi et al, 2021	4	10	5								
34	Ejaz et al, 2021	24	23	14	6							
35	Prasad et al, 2021	28			35							
36	Baqi et al, 2021	50	53	16						7		
37	Asghar et al, 2021	4	6	1	4	1		3				
38	Chachar et al, 2021	23	20	7	7			5	9	2		
39	Karthi et al, 2021			1								
40	Muttineni et al, 2021	32	31	9	8			4			5	
41	Hussain et al, 2020	2	2									
42	Khalid et al, 2021	13	22	11		9		2				
43	Lamech et al, 2021	11	18	5	24			1				
44	Meshram et al, 2021	5	5		16							
45	Pednekar et al, 2022	86	92									
46	Bhinder et al, 2021	26	46	4	52			4			5	
47	Pranshu et al, 2022	7	5		1			1			2	
48	Jamir et al, 2021	34	27					9		69		
49	Asghar et al, 2022	15	2	1	2			1	15			
50	Roy et al, 2021	24	31	2	4			4			8	
51	Singh et al, 2021	5	7									
52	Anand et al, 2022	22	22	9	4			9	3		4	
53	Asaduzzaman et al, 2022	33	33	20	14		4	31				

54	Parvin et al, 2022	89	109	18	26	5		20	9			
55	Rana et al, 2022	178	176		112							
56	Parhad et al, 2022	266	289	77	77	17		20	13	6	27	14
57	Dravid et al, 2022	14	7	3	3	2	1			1	1	
58	Kantroo et al, 2021	34	28	16	17		4	3	9			
59	Prakash et al, 2020	1	1									
60	Akhtar et al, 2021	245	294	135	52			63	8			18
61	Alam et al, 2022	31	40	10	10	3		6				
62	Asaduzzaman et al, 2022	42	41	23	19		5	13				
63	Vardhan et al, 2021	117	147	41	172			13				
64	Rai et al, 2021	121	122	21	31			16	8		26	
65	Zirpe et al, 2021	10	3	1	3							
66	Mittal et al, 2022	581	306	102	95	21		8				
67	Thakare et al, 2022	39	54	14	58		9					
68	Yadla et al, 2021	25	35		36							
69	Desai et al, 2021	6	4	2	2				2			2
70	Nigam et al, 2021	21	21	3	6	4		2	2			
71	Kayina et al, 2020	3	3		3	2			2			
72	Banerjee et al, 2021				22							
73	Choudhary et al, 2022	12	28		30							
74	Haroon et al, 2022	23	27	18				4				
75	Chowdhury et al, 2022	15	13	8	1			5				
76	Chopra et al, 2022	12	14	3				5		12		
77	Bansode et al, 2022	44	37	9	11		3	1				

78	Budhiraja et al, 2021	17	59	24							14	
79	Ramaswamy et al, 2020	5	13						23			
80	Elavarasi et al, 2021	129	128	34	10	1		18	27		23	4
81	Kute et al, 2020	15	25	5	29							
82	Mohan et al, 2020	1						1				
83	de Souza et al, 2020	33	33	8	5	1		5	5			
84	Havaldar et al, 2022	39	38	14	10	3	3	5	2			
85	Parry et al, 2020	1				1						
86	Mohandas et al, 2021	92	82	33	11			4				
87	Shankar et al, 2021	15	1		31							
88	Rao et al, 2021								4			
89	Mahapatra et al, 2022	6	14	4	17							
90	Bhandari et al, 2021	1	4	2	5							
91	Dosi et al, 2020	11	10	3	3			5		1	1	

Table 2c: Reported comorbidities of the deceased population of the selected study articles

Pediatric Population

Table 3 (a, b, c) lists the 6 studies which were conducted explicitly on a population which was below 14 years of age. These 6 studies were separated from the rest of the studies as the pediatric populations have unique characteristics and physiologies that may be different from adults. Therefore, the impact of comorbidities on the outcome of COVID-19 infection may be different in pediatric populations compared to adults. Pediatric populations may have different comorbidities than adults, so it is important to understand the specific comorbidities that are most common and how they impact the outcome of COVID-19 infection in pediatric populations. The management of pediatric patients with comorbidities is different from adult patients, so it is important to study these conditions separately.

SL #	References	Study Location	Study Design	Method	Number of participants	Gender		Number of deceased participants	Gender	
						M	F		M	F
1	Sharma et al, 2021	New Delhi - India	hospital based retrospective chart review	RT-PCR/CBNAAT	100	59	41	27	16	11
2	Jat et al, 2021	India	hospital based retrospective	RT-PCR / CBNAAT	402	247	155	13	Not mentioned	
3	Sarkar et al, 2022	Eastern India	hospoital based - descriptive study	RT-PCR	128			3	Not mentioned	
4	Ch et al, 2020	Lahore - Pakistan	hospital based cross sectional study	RT-PCR	42	19	23	3	Not mentioned	
5	Karthi et al, 2021	Chandigarh - India	hospital based - retrospective study	RT PCR	31	16	15	1	Not mentioned	
6	Rao et al, 2021	India	hospital based retrospective study	RT-PCR	123	71	52	14	Not mentioned	

Table 3a: Characteristics of studies based on population under 14 years of age

SL #	References	Reported comorbidities on COVID patients										
		DM	HT	CVD	CKD	CLD	CVA	COPD/ BA	Cancer	Obesity	Thyroid	NSD
1	Sharma et al, 2021								13			
2	Jat et al, 2021			24	13			7	36			10
3	Sarkar et al, 2022			4					2			3
4	Ch et al, 2020	1		2	7	1			2			1
5	Karthi et al, 2021			2	1							3
6	Rao et al, 2021			7	5				3			

Table 3b: Reported comorbidities of overall population under 14 years of age

SL #	References	Reported comorbidities on deceased COVID patients										
		DM	HT	CVD	CKD	CLD	CVA	COPD/ BA	Cancer	Obesity	Thyroid	NSD
1	Sharma et al, 2021								2			
2	Jat et al, 2021			5	1				1			5
3	Sarkar et al, 2022			1					1			1
4	Ch et al, 2020				1	1			1			
5	Karthi et al, 2021			1								
6	Rao et al, 2021								4			

Table 3c: Reported comorbidities of the deceased population under 14 years of age

Studies that represent population that are conducted on COVID-19 patients only vs studies that studies that represent population that are conducted on COVID-19+comorbid patients

There were 64 studies conducted on COVID-19 patients only - these 64 studies have been separated in Table 4 (a, b, c) and there were 27 studies conducted on a population where the whole sample size had a particular comorbidity, such as diabetes, cancer, etc. along with COVID-19 (Table 5 a, b, c).

Studies that focus on the general COVID-19 population provide a baseline for understanding the impact of COVID-19 on the general population. By comparing this baseline to studies that focus on the COVID-19 population with comorbidities, it allows for a better understanding of how comorbidities impact the outcome of COVID-19 infection. By separating the studies based on the presence or absence of comorbidities, it allows for a more specific analysis of the impact of each comorbidity on the outcome of COVID-19 infection.

Among the 27 studies which was based on a specific comorbid population, 1 study was conducted on COVID-19 patients with a history of cerebrovascular accidents, 1 study on COVID-19 patients with cardiovascular diseases, 2 studies were conducted on COVID-19 infected diabetic patients, 2 studies on COVID-19 CAM patients, 2 studies on COVID-19 AKI patients, 4 studies conducted on COVID-19 cancer patients and 16 studies were conducted on COVID-19 infected patients with a history of chronic kidney diseases.

SL #	References	Study Location	Study Design	Method	Number of participants	Gender		Number of deceased participants	Gender	
						M	F		M	F
1	Padmaprakash et al, 2021	Northern India	hospital-based cohort study	RT-PCR	1536	1357	179	76	59	17
2	Saha et al, 2021	Chittagong - Bangladesh	hospital-based retrospective study	RT-PCR	168	134	34	95	75	20
3	Islam et al, 2020	Dhaka - Bangladesh	Retrospective Cohort study	RT-PCR	1016	651	365	25	19	6
4	Mowla et al, 2020	Dhaka - Bangladesh	Retrospective - cross sectional study	RT-PCR	100	63	37	10	10	0
5	Hossain et al, 2021	Dhaka - Bangladesh	hospital based cross sectional study	RT-PCR/HRCT	486	306	180	94	66	28
6	Soni et al, 2021	Chandigarh - India	hospital based study	RT-PCR	114	66	48	3	Not mentioned	
7	Bobdey et al, 2021	Maharastra - India	hospital based-retrospective study	RT-PCR	1233	984	249	72	50	22
8	Gupta et al, 2020	New Delhi - India	hospital based prospective - study	RT-PCR	200	116	84	19	Not mentioned	
9	Sharma et al, 2021	New Delhi - India	hospital based retrospective chart review	RT-PCR/CBNAAT	100	59	41	27	16	11
10	Malik et al, 2020	Dhaka - Bangladesh	hospital based - cross sectional study	RT-PCR	139	57	82	1	Not mentioned	
11	Vadiraj et al, 2022	New Delhi - India	hospital based retrospec	RT-PCR	708	561	147	96	Not mentioned	

			tive cohort study							
12	Jat et al, 2021	India	hospital based retrospec tive	RT-PCR / CBNAA T	402	247	155	13	Not mentioned	
13	Sarkar et al, 2022	Eastern India	hospoital based - descripti ve study	RT-PCR	128			3	Not mentioned	
14	Akhtar et al, 2021	Rawalpin di-Islamaba d, Pakistan	Retrospe ctive observati onal study	PCR	1812	1253	559	469	313	15 6
15	Nasir et al, 2021	Karachi - Pakistan	hospital based observati onal study	RT-PCR	445	298	147	58	47	11
16	Ayaz et al, 2020	Karachi - Pakistan	hospital based retrospec tive cohort study	RT-PCR	66	40	26	9	9	0
17	Ch et al, 2020	Lahore - Pakistan	hospital based cross sectional study	RT-PCR	42	19	23	3	Not mentioned	
18	Haq et al, 2020	Khyber Pakhtunk hwa - Pakistan	hospital based retrospec tive cohort study	RT-PCR	179	150	29	52	38	14
19	Jayaswal et al, 2021	New Delhi - India	hospital based retrospec tive case control study	RT-PCR/R AT	813	559	254	52	Not mentioned	
20	Gupte et al, 2022	Various states - India	hospital based-retrospec tive	RT-PCR	2329	1570	583	134	108	26
21	Mammen et al, 2021	India	Randomi zed Controlle d Trial	RT-PCR	451	346	105	65	52	13

22	Sharif et al, 2021	Bangladesh - clinics from eight division	hospital based - retrospective	RT-PCR	799	526	273	318	Not mentioned	
23	Gupta et al, 2021	Kolkata - India	hospital based - prospective	RT - PCR	710	530	180	50	Not mentioned	
24	Gopalan et al, 2022	Tamil Nadu - India	hospital based - retrospective study	RT-PCR	746	466	280	259	173	86
25	Rehman et al, 2021	Islamabad - Pakistan	hospital based - retrospective	RT-PCR	2048	1217	831	590	415	175
26	Ejaz et al, 2021	Karachi - Pakistan	hospital based - Retrospective	RT-PCR	71	62	9	41	Not mentioned	
27	Baqi et al, 2021	Karachi - Pakistan	hospital based - observational study	PCR	252	188	64	95	68	27
28	Chachar et al, 2021	Lahore - Pakistan	hospital based - retrospective study	PCR	428	291	154	37	23	14
29	Karthi et al, 2021	Chandigarh - India	hospital based - retrospective study	RT PCR	31	16	15	1	Not mentioned	
30	Muttineni et al, 2021	Hyderabad, India.	hospital based	RT-PCR	109	78	31	52	41	11
31	Hussain et al, 2020	Karachi - Pakistan	hospital based descriptive case series	RT-PCR	266	238	28	18	Not mentioned	
32	Khalid et al, 2021	Punjab - Pakistan	hospital based retrospective study	RT-PCR	317	198	111	57	Not mentioned	
33	Pednekar et al, 2022	Maharashtra - India	hospital based - retrospective study	Antigen test/RT-PCR/CBNAAT	231	150	81	92	56	36

34	Pranshu et al, 2022	Rajashtan - India	hospital based retrospective	RT-PCR	65	41	24	12	10	2
35	Jamir et al, 2021	Andhra Pradesh - India	hospital based retrospective	RT-PCR	266	259	7	101	98	3
36	Roy et al, 2021	New Delhi - India	hospital based retrospective observational study	RT-PCR/CB-NAAT	141	80	61	54	32	22
37	Singh et al, 2021	Bihar - India	hospital based cross-sectional study	RT-PCR	156	118	38	18	16	2
38	Anand et al, 2022	Kerala - India	hospital based retrospective study	RT-PCR	476	265	211	30	20	10
39	Asaduzzaman et al, 2022	Sylhet - Bangladesh	hospital based retrospective study	RT-PCR	245	158	87	43	26	17
40	Parvin et al, 2022	Dhaka - Bangladesh	hospital based cross-sectional study	RT-PCR	972	624	348	161	127	34
41	Rana et al, 2022	Delhi - India	hospital based retrospective study	RT-PCR	2586	1800	786	317	Not mentioned	
42	Parhad et al, 2022	Raipur - India	hospital based retrospective study	RT-PCR/RAT/True NAT	5552	3557	1995	559	430	129
43	Kantroo et al, 2021	Delhi - India	hospital based retrospective study	RT-PCR	1192	832	360	73	55	18
44	Prakash et al, 2020	Uttar Pradesh - India	hospital based retrospective observational study	PCR	17	15	2	1	1	0

45	Akhtar et al, 2021	Islamabad - Pakistan	hospital based retrospective study	PCR	659	452	207	469	313	156
46	Alam et al, 2022	Karachi - Pakistan	hospital based retrospective study	RT-PCR	209	149	60	60	42	18
47	Asaduzzaman et al, 2022	Sylhet - Bangladesh	hospital based retrospective study	PCR/radiography	442	291	151	55	34	21
48	Rai et al, 2021	Patna - India	hospital based retrospective observational study	RT-PCR/RAT	984	762	222	254	203	51
49	Mittal et al, 2022	Panjab - India	hospital based retrospective observational study	RT-PCR	4559	3005	1554	967	Not mentioned	
50	Desai et al, 2021	Ahmedabad - India	hospital based retrospective observational study	RT-PCR	112	80	32	15	10	5
51	Nigam et al, 2021	Patna - India	hospital based descriptive study	RT-PCR	252	179	73	46	37	9
52	Kayina et al, 2020	Delhi - India	hospital based prospective observational study	RT-PCR	235	160	85	20	14	6
53	Haroon et al, 2022	Karachi - Pakistan	hospital based retrospective study	RT-PCR	102	58	44	38	22	16
54	Chowdhury et al, 2022	Chittagong - Bangladesh	clinical trial study	RT-PCR	208	155	53	57	38	19

55	Chopra et al, 2022	Kolkata - India	hospital based retrospective observational cross-sectional study	RT-PCR	83	45	38	36	21	15
56	Budhiraja et al, 2021	Delhi - India	multicenter retrospective observational case control study	RT-PCR	361	361	261	100	73	47
57	Elavarasi et al, 2021	Jhajjar-India	hospital based retrospective study	RT-PCR/NAAT/RAT	2017	1320	697	406	274	132
58	Mohan et al, 2020	India	hospital based prospective study	RT-PCR	144	134	10	2	2	0
59	de Souza et al, 2020	Mumbai - India	hospital based observational study	RT-PCR	689	338	351	156	94	62
60	Havaldar et al, 2022	India	multicenter cohort study	RT-PCR	174	121	53	76	56	20
61	Parry et al, 2020	Kashmir - India	hospital based prospective observational study	RT-PCR	147	104	43	2	Not mentioned	
62	Mohandas et al, 2021	Tamil Nadu - India	hospital based retrospective study	RT-PCR/Radiography	3345	2314	1031	142	111	31
63	Rao et al, 2021	India	hospital based retrospective study	RT-PCR	123	71	52	14	Not mentioned	
64	Dosi et al, 2020	Madhya Pradesh - India	hospital based retrospective study	RT-PCR	365	212	153	31	21	10

Table 4a: Characteristics of studies based on COVID-19 population only

SL #	References	Reported comorbidities on COVID patients										
		DM	**HT**	**CVD**	**CKD**	**CLD**	**CVA**	**COPD/ BA**	**Cancer**	**Obesity**	**Thyroid**	**NSD**
1	Padmaprakash et al, 2021	103	130	49	15	3	11	8	45			
2	Saha et al, 2021	88	69	28	5			15				
3	Islam et al, 2020	179	145	40	21	13		85	9			
4	Mowla et al, 2020	16	21	8	8	3	1	6	2	5		
5	Hossain et al, 2021	192	201	37	20	6		53	12			
6	Soni et al, 2021	17	19	2	3	1	1	2		1		
7	Bobdey et al, 2021	45	53									
8	Gupta et al, 2020	32	46	9	4		5	1	5		6	
9	Sharma et al, 2021								13			
10	Malik et al, 2020	10	21	6				10				
11	Vadiraj et al, 2022	130	126	54	13		6	19	36			
12	Jat et al, 2021			24	13			7	36			10
13	Sarkar et al, 2022			4					2			3
14	Akhtar et al, 2021	532	625	243	93			111	13			30
15	Nasir et al, 2021	162	167	74	31	8	10		22			
16	Ayaz et al, 2020	25	30	10	3			2	4			
17	Ch et al, 2020	1		2	7	1			2			1
18	Haq et al, 2020	48	62	29	3		2	27				
19	Jayaswal et al, 2021	236	223									
20	Gupte et al, 2022	679	465	145				100				
21	Mammen et al, 2021	196	169	31	17		4	15		31		
22	Sharif et al, 2021	261		337	78			104	30	144		
23	Gupta et al, 2021	53	87	49	39			21	50			37

24	Gopalan et al, 2022	299	219	75	72	8		35	10	10		
25	Rehman et al, 2021	608	975	1177	68	79	629	289	50			
26	Ejaz et al, 2021	39	39	24	9							
27	Baqi et al, 2021	132	128	37						22		
28	Chachar et al, 2021	168	195	61	29			54	9	51		
29	Karthi et al, 2021			2	1							3
30	Muttineni et al, 2021	37	34	10	8			5			5	
31	Hussain et al, 2020	36	48	24	2			8	2			
32	Khalid et al, 2021	112	124	28		40		13				
33	Pednekar et al, 2022	141	179	24	4	12	8	12		82	10	
34	Pranshu et al, 2022	21	21	4	2			2			5	
35	Jamir et al, 2021	100	77					14		200		
36	Roy et al, 2021	53	58	7	8			2			18	
37	Singh et al, 2021	17	16									
38	Anand et al, 2022	214	209	60	17			36	9		56	
39	Asaduzzaman et al, 2022	175	195	75	56		18	32				
40	Parvin et al, 2022	410	424	76	46	14		109	22			
41	Rana et al, 2022	1002	903		170							
42	Parhad et al, 2022	1410	1649	322	241	53		81	87	17	299	61
43	Kantroo et al, 2021	319	335	78	96		17	31	46			
44	Prakash et al, 2020	5	2	1				1				
45	Akhtar et al, 2021	331	377	163	57			74	8			20
46	Alam et al, 2022	84	105	27	25	12		23				
47	Asaduzzaman et al, 2022	281	311	98	78		20	54				
48	Rai et al, 2021	330	306	57	53			37	18		93	

49	Mittal et al, 2022	2090	1079	268	215	69		19				
50	Desai et al, 2021	19	37	13	6			13	4			9
51	Nigam et al, 2021	86	98	20	17	9		15	6			
52	Kayina et al, 2020	54	65	13	22	10		5	26			
53	Haroon et al, 2022	57	58	28				9				
54	Chowdhury et al, 2022	28	38	15	2		3	12	1		4	
55	Chopra et al, 2022	23	26	5				8		19		
56	Budhiraja et al, 2021	66	157	51							33	
57	Elavarasi et al, 2021	437	457	96	25	5		54	102		86	29
58	Mohan et al, 2020	16	3	1				3			3	1
59	de Souza et al, 2020	67	66	17	20	2		11	10			
60	Havaldar et al, 2022	70	62	18	10	5	3	11	4			
61	Parry et al, 2020	5	9			1						
62	Mohandas et al, 2021	1240	974	200	52			105			94	
63	Rao et al, 2021			7	5				3			
64	Dosi et al, 2020	82	92	14	9			13	2	5	11	

Table 4b: Reported comorbidities of the COVID-19 population

SL #	References	Reported comorbidities on deceased COVID patients										
		DM	**HT**	**CVD**	**CKD**	**CLD**	**CVA**	**COPD/ BA**	**Cancer**	**Obesity**	**Thyroid**	**NSD**
1	Padmaprakash et al, 2021	23	28	11	4	2		2	11			
2	Saha et al, 2021	53	41	23	3			3				
3	Islam et al, 2020	9	9	4	4	3		10	2			
4	Mowla et al, 2020	4	5	4	4			2	1			
5	Hossain et al, 2021	44	49	11	8	3		9	4			

6	Soni et al, 2021	3			2							
7	Bobdey et al, 2021	34	32									
8	Gupta et al, 2020	8	8	1					1			
9	Sharma et al, 2021								2			
10	Malik et al, 2020			1								
11	Vadiraj et al, 2022	34	31	15	2		3	5	12			
12	Jat et al, 2021			5	1				1			5
13	Sarkar et al, 2022			1					1			1
14	Akhtar et al, 2021	245	294	135	56			69	9			21
15	Nasir et al, 2021	28	31	20	12				7			
16	Ayaz et al, 2020	8	8	6	3				2			
17	Ch et al, 2020				1	1			1			
18	Haq et al, 2020	24	31	19	2		2	13				
19	Jayaswal et al, 2021	29	17									
20	Gupte et al, 2022	62	23	19				10				
21	Mammen et al, 2021	32	30	8	6		1	5		6		
22	Sharif et al, 2021	237		288								
23	Gupta et al, 2021	16	21	5	11			5	5			10
24	Gopalan et al, 2022	145	106	42	50	7		11	8	8		
25	Rehman et al, 2021	395	444	202	20	41	310	143	21			
26	Ejaz et al, 2021	24	23	14	6							
27	Baqi et al, 2021	50	53	16						7		
28	Chachar et al, 2021	23	20	7	7			5	9	2		
29	Karthi et al, 2021			1								
30	Muttineni et al, 2021	32	31	9	8			4			5	
31	Hussain et al, 2020	2	2									

32	Khalid et al, 2021	13	22	11		9		2				
33	Pednekar et al, 2022	86	92									
34	Pranshu et al, 2022	7	5		1			1			2	
35	Jamir et al, 2021	34	27					9		69		
36	Roy et al, 2021	24	31	2	4			4			8	
37	Singh et al, 2021	5	7									
38	Anand et al, 2022	22	22	9	4			9	3		4	
39	Asaduzzaman et al, 2022	33	33	20	14		4	31				
40	Parvin et al, 2022	89	109	18	26	5		20	9			
41	Rana et al, 2022	178	176		112							
42	Parhad et al, 2022	266	289	77	77	17		20	13	6	27	14
43	Kantroo et al, 2021	34	28	16	17		4	3	9			
44	Prakash et al, 2020	1	1									
45	Akhtar et al, 2021	245	294	135	52			63	8			18
46	Alam et al, 2022	31	40	10	10	3		6				
47	Asaduzzaman et al, 2022	42	41	23	19		5	13				
48	Rai et al, 2021	121	122	21	31			16	8		26	
49	Mittal et al, 2022	581	306	102	95	21		8				
50	Desai et al, 2021	6	4	2	2				2			2
51	Nigam et al, 2021	21	21	3	6	4		2	2			
52	Kayina et al, 2020	3	3		3	2			2			
53	Haroon et al, 2022	23	27	18				4				
54	Chowdhury et al, 2022	15	13	8	1			5				
55	Chopra et al, 2022	12	14	3				5		12		

56	Budhiraja et al, 2021	17	59	24							14	
57	Elavarasi et al, 2021	129	12 8	34	10	1		18	27		23	4
58	Mohan et al, 2020	1						1				
59	de Souza et al, 2020	33	33	8	5	1		5	5			
60	Havaldar et al, 2022	39	38	14	10	3	3	5	2			
61	Parry et al, 2020	1				1						
62	Mohandas et al, 2021	92	82	33	11			4				
63	Rao et al, 2021								4			
64	Dosi et al, 2020	11	10	3	3			5		1	1	

Table 4c: Reported comorbidities of the deceased COVID-19 population

SL #	References	Study Location	Study Design	Method	Number of participants	Gender		Number of deceased participants	Gender	
						M	F		M	F
1	Mehta et al, 2021	Delhi - India	hospital based retrospective cohort study	RT-PCR	186	105	81	27	16	11
2	Mathew et al, 2021	Bengaluru - India	hospital based - retrospective	RT - PCR	62	48	14	13	10	3
3	Chandrasekaran et al, 2021	Chennai - India	hospital based retrospective cohort study	RT - PCR and CT	102	73	29	33	24	9
4	Sindhu et al, 2021	South India	hospital based retrospective	PCR	190	155	35	42	35	7
5	Kunal et al, 2020	India - Rajasthan	hospital based - retrospective	RT - PCR	108	70	38	30	19	11
6	Kute et al, 2021	Ahmedabad - India	hospital based -	RT-PCR	157	133	24	15	14	1

			Retrospective							
7	Sinha et al, 2021	Mumbai - India	hospital based - prospective	RT - PCR	131	75	56	27	17	10
8	Kazmi et al, 2021	Karachi - Pakistan	hospital based - retrospective study	RT-PCR	43	25	18	11	8	3
9	Prasad et al, 2021	India	hospital based prospective - study	RT-PCR	263	173	90	35	27	8
10	Asghar et al, 2021	Lahore and Peshawar - Pakistan	hospital based - retrospective cohort study	PCR	70	38	32	30	19	11
11	Lamech et al, 2021	Chennai - India	hospital based prospective study	RT-PCR	183	118	65	24	Not mentioned	
12	Meshram et al, 2021	India	hospital based - retrospective cohort study	RT-PCR	61	54	7	16	15	1
13	Bhinder et al, 2021	Delhi - India	hospital based - retrospective study	RT-PCR	213	132	81	52	33	19
14	Asghar et al, 2022	Lahore - Pakistan	hospital based retrospective	RT-PCR	43	26	17	15	9	6
15	Dravid et al, 2022	Pune - India	hospital based retrospective study	RT-PCR/RAT	59	47	12	15	11	4
16	Vardhan et al, 2021	Patna - India	hospital based retrospective observational study	RT-PCR	261	195	66	172	Not mentioned	
17	Zirpe et al, 2021	Pune - India	hospital based retrospective observational study	RT-PCR	84	70	14	13	13	0

18	Thakare et al, 2022	Mumbai - India	hospital based observational study	RT-PCR	234	152	82	76	54	22
19	Yadla et al, 2021	Hyderabad - India	hospital based observational study	RT-PCR	84	57	27	36	23	13
20	Banerjee et al, 2021	Gujarat - India	hospital based retrospective study	RT-PCR	58	32	26	22	Not mentioned	
21	Choudhary et al, 2022	India	hospital based retrospective study	RT-PCR	218	169	49	30	23	7
22	Bansode et al, 2022	Maharashtra - India	hospital based prospective observational study	RT-PCR	111	75	36	58	36	22
23	Ramaswamy et al, 2020	Mumbai - India	hospital based observational study	RT-PCR	230	124	106	23	10	13
24	Kute et al, 2020	India	multicenter cohort study	RT-PCR	250	215	35	29	26	3
25	Shankar et al, 2021	South India	hospital based cross-sectional observational study	RT-PCR	90	60	30	31	20	11
26	Mahapatra et al, 2022	India	hospital based case series	RT-PCR	44	20	24	17	Not mentioned	
27	Bhandari et al, 2021	India	hospital based observational study	RT-PCR	20	17	3	5	4	1

Table 5a: Characteristics of studies based on COVID-19+Comorbid population

SL #	References	Reported comorbidities on COVID patients										
		DM	**HT**	**CVD**	**CKD**	**CLD**	**CVA**	**COPD/ BA**	**Cancer**	**Obesity**	**Thyroid**	**NSD**
1	Mehta et al, 2021	34	45	11				2	186		30	
2	Mathew et al, 2021	34	38	5								
3	Chandrasekaran et al, 2021		53	10	10	10	8			27		
4	Sindhu et al, 2021	137	127	57	43		10					
5	Kunal et al, 2020	35	41	14	9			14	3			
6	Kute et al, 2021	38	114	17	157					38		
7	Sinha et al, 2021	38	99	29				11			6	
8	Kazmi et al, 2021	14	35	12								
9	Prasad et al, 2021	142			263							
10	Asghar et al, 2021	9	14	3	7	3		8				
11	Lamech et al, 2021	62	140	45	118			11				
12	Meshram et al, 2021	15	19		61							
13	Bhinder et al, 2021	75	177	19	213	2		4			11	
14	Asghar et al, 2022	43	11	3	3	1		2	43			
15	Dravid et al, 2022	53	24	7	9	2	1			2	3	
16	Vardhan et al, 2021	187	222	60	261			21				
17	Zirpe et al, 2021	54	31	4	3							
18	Thakare et al, 2022	96	180	20	199		16					
19	Yadla et al, 2021	45	79	7	84		2	1				
20	Banerjee et al, 2021	11	38	9	58							
21	Choudhary et al, 2022	56	200		218							
22	Bansode et al, 2022	71	72	19	25		6	5				

23	Ramaswamy et al, 2020	30	25	2					230			
24	Kute et al, 2020	80	210	30	250							
25	Shankar et al, 2021	31	1		90							
26	Mahapatra et al, 2022	10	37	7	44							
27	Bhandari et al, 2021	11	19	3	20							

Table 5b: Reported comorbidities of the COVID-19+Comorbid population

SL #	References	Reported comorbidities on deceased COVID patients										
		DM	**HT**	**CVD**	**CKD**	**CLD**	**CVA**	**COPD/ BA**	**Cancer**	**Obesity**	**Thyroid**	**NSD**
1	Mehta et al, 2021	10	9	4					27		4	
2	Mathew et al, 2021	10	11	2								
3	Chandrasekaran et al, 2021		19	6	5	6	3			10		
4	Sindhu et al, 2021	35	31	19	10		3					
5	Kunal et al, 2020	14	17	5								
6	Kute et al, 2021	5	10	3	15					8		
7	Sinha et al, 2021	15	22	9				3				
8	Kazmi et al, 2021	4	10	5								
9	Prasad et al, 2021	28			35							
10	Asghar et al, 2021	4	6	1	4	1		3				
11	Lamech et al, 2021	11	18	5	24			1				
12	Meshram et al, 2021	5	5		16							
13	Bhinder et al, 2021	26	46	4	52			4			5	
14	Asghar et al, 2022	15	2	1	2			1	15			
15	Dravid et al, 2022	14	7	3	3	2	1			1	1	

16	Vardhan et al, 2021	117	147	41	172			13				
17	Zirpe et al, 2021	10	3	1	3							
18	Thakare et al, 2022	39	54	14	58		9					
19	Yadla et al, 2021	25	35		36							
20	Banerjee et al, 2021				22							
21	Choudhary et al, 2022	12	28		30							
22	Bansode et al, 2022	44	37	9	11		3	1				
23	Ramaswamy et al, 2020	5	13						23			
24	Kute et al, 2020	15	25	5	29							
25	Shankar et al, 2021	15	1		31							
26	Mahapatra et al, 2022	6	14	4	17							
27	Bhandari et al, 2021	1	4	2	5							

Table 5c: Reported comorbidities of the deceased COVID-19+Comorbid population

Study Locations

Figure 6 shows the map of South Asia displaying the city wise locations for the selected studies, as well as the total sample population of this review. Table 6 shows the prevalence and mortality of COVID-19 patients in the three countries of interest. These studies yielded a total sample size of 48908 patients - of which 37281 (76.23%) were from India, 4575 (9.35%) were from Bangladesh and 7052 (14.42%) were from Pakistan. The highest proportion of studies was conducted in Delhi, India (n=11), followed by Karachi, Pakistan (n=8). Selected studies were published in 3 different locations in Bangladesh, 5 in Pakistan and 17 in India. The specific locations in Bangladesh were Dhaka, Chittagong and Sylhet, while the specific locations in Pakistan were Karachi, Faisalabad, Lahore, Islamabad and Peshawar. The city locations in India were grouped according to the various states in India - Delhi, Tamil Nadu, Kerala, Karnataka, Andhra Pradesh, Madhya Pradesh, Uttar Pradesh, West Bengal, Haryana, Maharashtra, Punjab, Kashmir, Rajasthan, Gujarat, Bihar, Telangana and Chattisgarh.

In all three countries, there was a higher proportion of male participants compared to females. Overall, in this review, there were 33314 males (68.15%) and 15570 females (31.85%). While information about gender in the overall COVID-19 population could be obtained for all the studies, some of the studies did not mention gender segregation in the COVID-19 deceased population. In total there were 22 out of 91 studies that did not mention the number of males and females in the deceased population. Among the studies, there were a total of 8198 COVID-19 related mortalities, among which 859 were from Bangladesh, 5287 from India and 2052 from Pakistan. Therefore, the overall mortality rate in this systematic review was 16.76%.

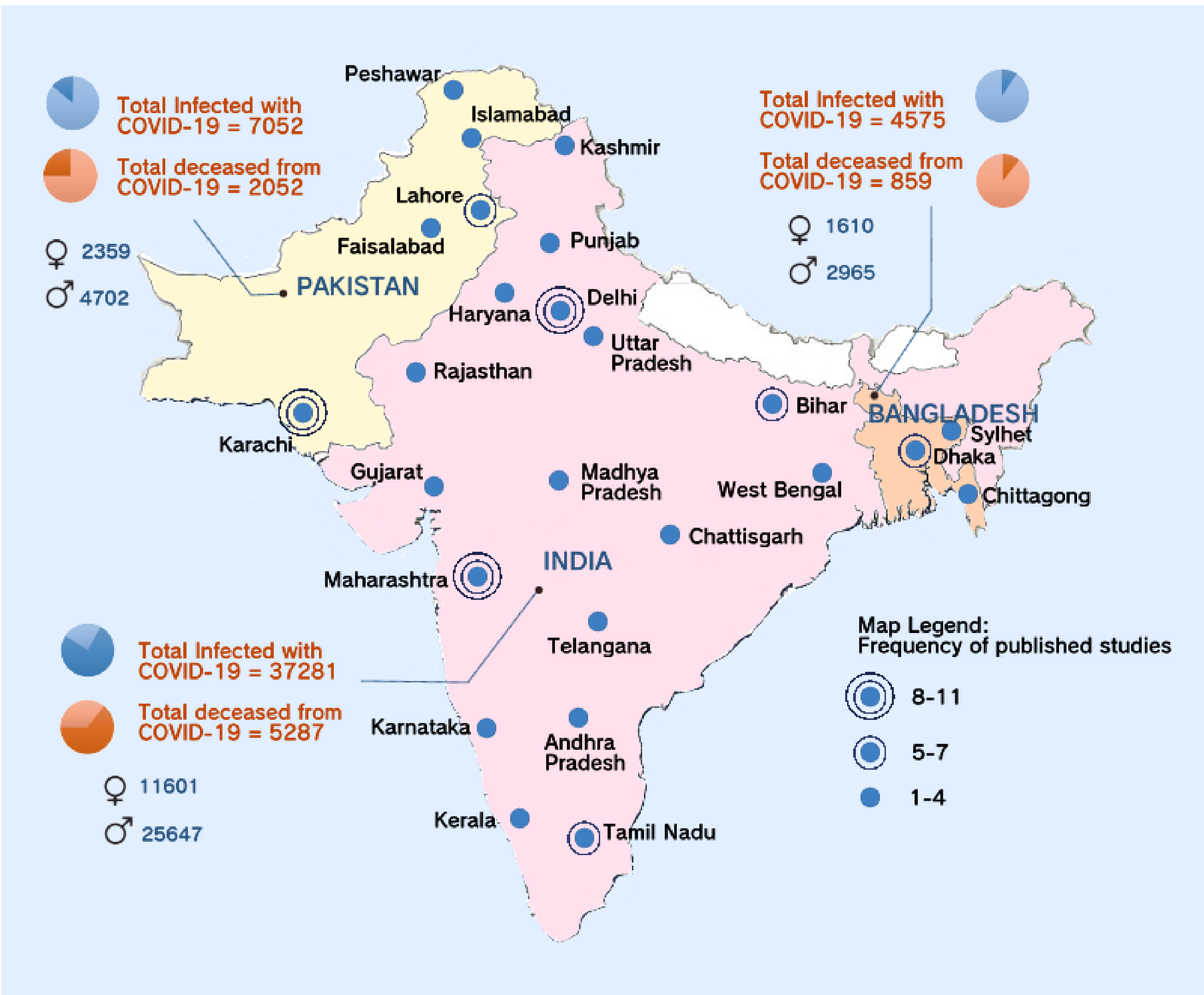

Figure 6: Location of the selected studies
[Ref: Original map from Free World Maps. https://www.freeworldmaps.net/asia/southasia/political.html]

Quality Assessment

According to Hoy et al., checklist studies [16] which score 0-3 will be considered low risk, 4-6 moderate risk and studies with score 7-9 will be considered as high risk of bias. Table of Risk of Bias assessment for selected studies is given in Table 7. Among these 91 studies, 13 studies were of high risk, 56 studies were of moderate risk and 22 studies were of low risk.

Author Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Quality Assessment
Padmaprakash et al - 2021	Yes	Not clear	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Saha et al - 2021	Not clear	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Islam et al - 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Mowla et al - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Hossain et al - 2021	Yes	Yes	Yes	Yes	Not clear	Not clear	Yes	Yes	Yes	Moderate Risk
Soni et al - 2021	Yes	Yes	No	Yes	Not clear	Yes	Yes	Yes	Not clear	Moderate Risk
Bobdey et al - 2021	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Moderate Risk
Mehta et al - 2021	No	Not clear	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Gupta et al - 2020	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	No	Moderate Risk
Sharma et al - 2021	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Malik et al - 2020	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Vadiraj et al - 2022	Yes	Not clear	Yes	Not clear	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Jat et al - 2021	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Sarkar et al - 2022	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Not clear	High Risk
Akhtar et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Nasir et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Ayaz et al - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Ch et al - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Haq et al - 2020	Yes	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Jayaswal et al - 2021	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Moderate Risk

Gupte et al - 2022	Not clear	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Mammen et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Mathew et al - 2021	No	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	High Risk
Chandrasekaran et al - 2021	No	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	High Risk
Sindhu et al - 2021	Not clear	Yes	No	Not clear	Not clear	Yes	Not clear	Yes	Not clear	High Risk
Kunal et al - 2020	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Sharif et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Kute et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Gupta et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Sinha et al - 2021	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Not clear	High Risk
Gopalan et al - 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Rehman et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Kazmi et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Ejaz et al - 2021	Not clear	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Prasad et al - 2021	Not clear	Not clear	Not clear	Not clear	Yes	Yes	Yes	Yes	Yes	High Risk
Baqi et al. - 2021	No	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Asghar et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Chachar et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low risk
Karthi et al - 2021	Yes	Not clear	No	Not clear	Yes	Yes	Yes	Yes	Not clear	High Risk
Muttineni et al - 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Hussain et al. - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Not clear	Not clear	Moderate Risk
Khalid et al. - 2021	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Lamech et al - 2021	Not clear	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	High Risk
Meshram et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Pednekar et al - 2022	Yes	Yes	No	Yes	Yes	Not clear	Yes	Yes	Not clear	Moderate Risk
Bhinder et al - 2021	No	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	High Risk

Pranshu et al - 2022	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Jamir et al - 2021	Not clear	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Asghar et al - 2022	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Roy et al - 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Singh et al - 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Anand et al - 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Asaduzzaman et al - 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Parvin et al - 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Rana et al - 2022	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Parhad et al - 2022	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Moderate Risk
Dravid et al - 2022	No	No	No	Yes	Yes	Not clear	Not clear	Yes	Not clear	High Risk
Kantroo et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Prakash et al – 2020	Yes	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Akhtar et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Alam et al - 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Asaduzzaman et al - 2022	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not clear	Moderate Risk
Vardhan et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Rai et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Zirpe et al- 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Mittal et al - 2022	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Thakare et al - 2022	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Yadla et al - 2021	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Desai et al - 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Nigam et al - 2021	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Kayina et al - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Banerjee et al - 2021	No	Not clear	No	Yes	Yes	Yes	Yes	Yes	Not clear	High Risk

Choudhary et al - 2022	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Haroon et al - 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Chowdhury et al - 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Chopra et al - 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Bansode et al - 2022	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Budhiraja et al - 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Low Risk
Ramaswamy et al - 2020	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Elavarasi et al - 2021	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Kute et al - 2020	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Mohan et al - 2020	Yes	Not clear	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
de Souza et al - 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk
Havaldar et al - 2022	Yes	Yes	No	Not clear	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Parry et al - 2020	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not clear	Moderate Risk
Mohandas et al - 2021	Yes	Not clear	Yes	Yes	Yes	Not clear	Yes	Yes	Not clear	Moderate Risk
Shankar et al - 2021	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Not clear	High Risk
Rao et al - 2021	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Mahapatra et al - 2022	No	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes	Moderate Risk
Bhandari et al - 2021	No	Not clear	No	Not clear	Yes	Yes	Yes	Yes	Yes	High Risk
Dosi et al - 2020	Yes	Not clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk

Table 6: Quality assessment by Joanna Briggs Institute Prevalence Critical Appraisal Checklist

General Indicators of Severity among COVID-19 patients with Comorbidities:

A diversified range of clinical features is seen in COVID-19 patients, while a major proportion of the SARS-CoV-2 infections can be asymptomatic. The range of symptomatic diseases can also range from mild to severe. In those patients that do become symptomatic, most people with COVID-19 develop only mild to moderate disease. According to the Living Guidance for Clinical Management of COVID-19 by the World Health Organization, around 15% develop severe disease that can require oxygen support and 5% can have a critical disease outcome with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury [2].

Many studies have focused on establishing the risk factors associated with severity of COVID-19 outcomes. Older age is one of the well-established risk factors of the disease, where individuals over 50 years of age are at a greater risk [17]. Multiple studies have also connected the male sex to be at a greater risk than the female sex. Existing comorbidities have been known to exacerbate the symptoms of COVID-19. Mammen et al. [18] found that patients with multiple comorbidities had 2.25 times the risk of death in India, while Abbas [19] has reported that the presence of more than 2 comorbidities increased the risk of mortality and severity by almost 5 times in Pakistan.

Biological markers of COVID-19 severity have also been investigated. Arambepola et al. [20] reported that a lower count of absolute T lymphocytes is associated with severe viral infection, while Kute et al. [21] reported higher levels of inflammatory markers such as C-reactive protein, interleukin 6 and procalcitonin in COVID-19 patients. In comparison to survivors of the disease, the deceased population had a higher level of interleukin-6. In another study, Khatri et al. [22] investigated the role of elevated D-dimers in disease prognosis. Their results concluded that all patients with CKD and bronchial asthma had elevated D-dimer and most patients with diabetes had increased levels of D-dimer. Moreover, the majority of patients with an elevated level of this marker at admission had succumbed to the illness. Other markers of disease severity were an abnormality in chest radiography and intensive care/ventilator requirements. ICU requirement was also a significant factor associated with mortality [23].

It is important to note that people with a weakened immune system are more vulnerable to being infected by SARS-CoV-2 and the presence of pre-existing conditions such as diabetes and hypertension can reduce the immunity of a person to a great extent, thereby facilitating entry of the virus to lung cells using the angiotensin-converting enzyme-2 receptor [3]. ACE2 is the functional receptor of three human-infecting coronaviruses: NL-63, SARS-CoV, and SARS-CoV-2. The expression of this receptor is moderate in lung alveolar epithelium cells, high in enterocytes of the small intestine, and to a lesser extent in the vascular endothelial and smooth muscle in many organs such as brain, liver, kidney, bone marrow and skin. It is through this receptor that these organs provide an easy pathway for the entry of SARS-CoV-2, and the gene expression data suggests that more severe symptoms could develop upon SARS-CoV-2 infection particularly in the respiratory tract and the gut.

The conditions mentioned above are the widely reported risk factors that leads to a higher allostatic load and COVID-19 may either induce or aggravate these conditions by impacting ACE2 receptor, RAAS function, immune, hemostatic and nervous system damage, and major physiological systems [24].

Prevalence and mortality of resulting from comorbid conditions among COVID-19 patients in South Asia

Figure 7 shows the underlying medical conditions and its associated mortality in COVID-19 confirmed cases in Bangladesh, India and Pakistan. Comorbid conditions were included in the review if they appeared in 10 or more studies. The most commonly reported comorbidities were diabetes, hypertension, cardiovascular diseases and chronic kidney diseases in all three countries. The most prevalent comorbidity was diabetes, hypertension, heart diseases and kidney diseases. The same four comorbid conditions were also seen to be present among the reported comorbidities among the deceased population. Among the population of 48908 COVID-19 patients, there were 8198 non-survivors. The same four comorbid conditions were seen to be present predominantly among the deceased population - diabetes, hypertension, heart disease and kidney diseases. Besides these four comorbidities, other reported conditions were chronic liver diseases, brain diseases, lung diseases, cancer, obesity and hypo/hyperthyroidism. Besides this, there were more pre-existing illnesses that were mentioned less frequently such as anemia, allergies, hematological disorders, hormonal disorders, endocrine disorders, etc. However, as the frequency of these conditions were less than 10 in the selected study articles, they were not analyzed in this systematic review.

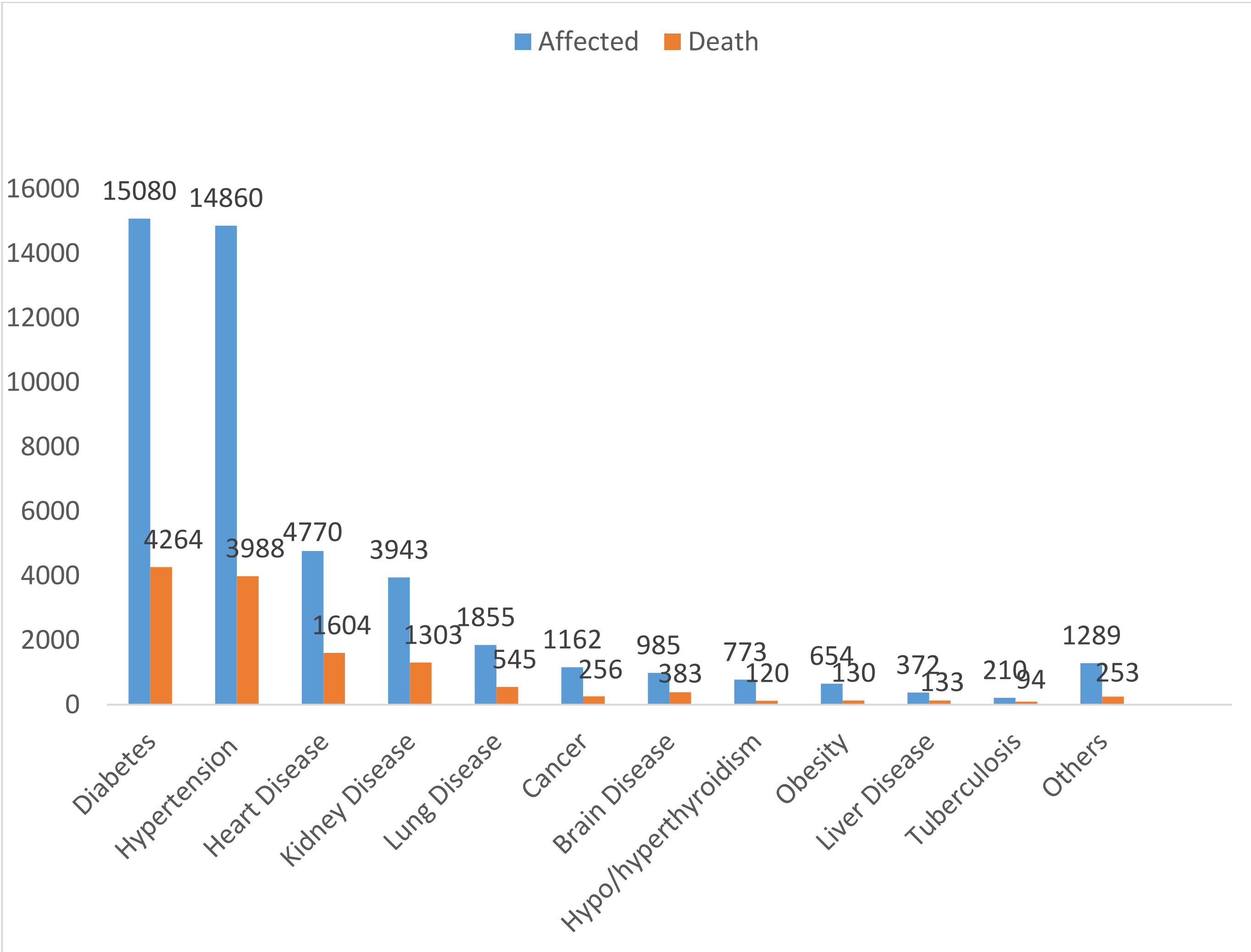

Fig 7: Underlying Medical Conditions and its Associated Mortality in COVID-19 Confirmed Cases in South

Figure 8 shows the prevalence and mortality of comorbidities in India among confirmed COVID-19 cases. The most prevalent comorbidity in India was found to be diabetes followed by hypertension - in both survived and non-survived population. The least prevalent comorbid condition was chronic liver diseases. For India, mortality was reported in association with all the comorbid conditions that were selected for analysis.

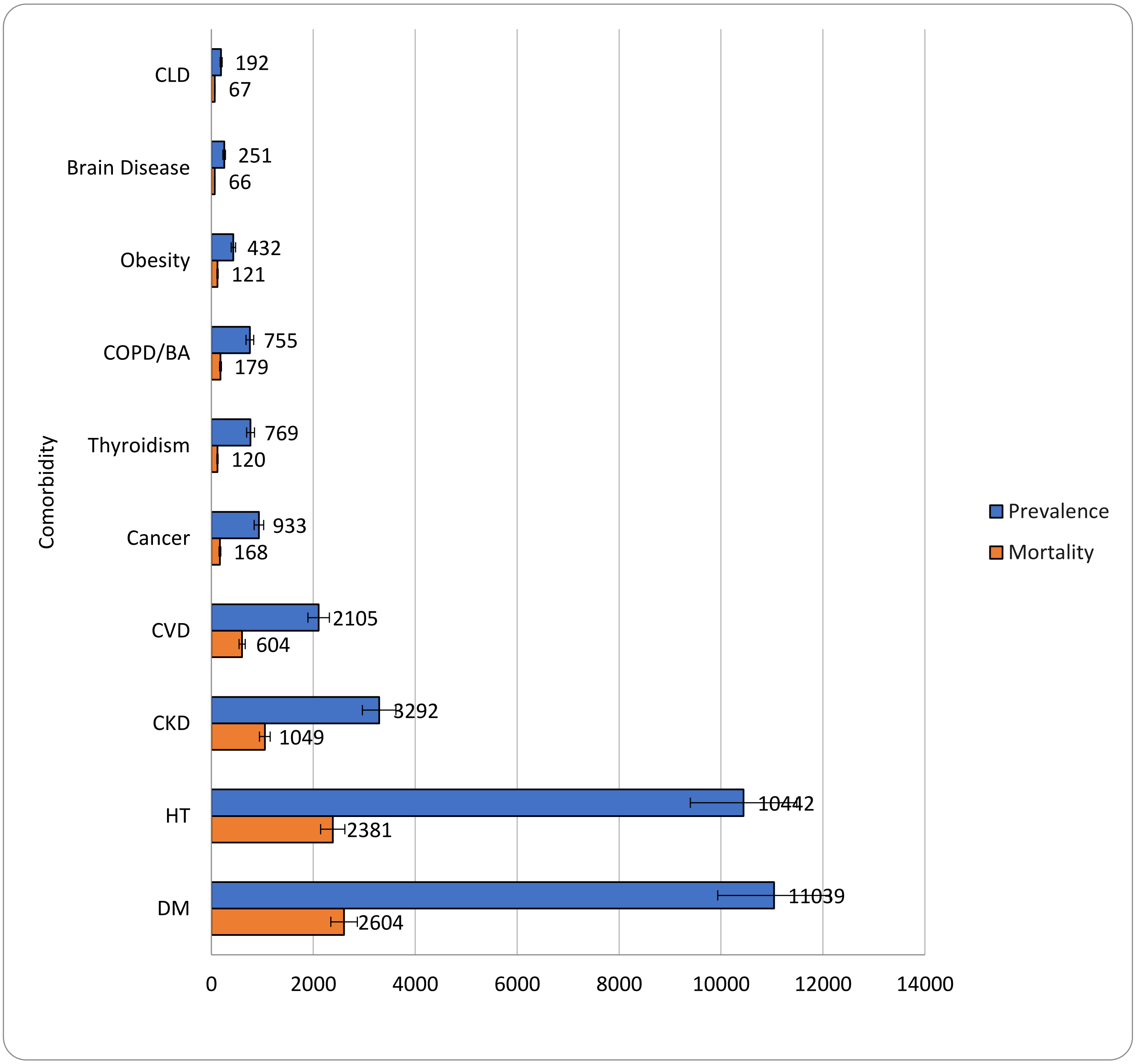

Fig 8: Prevalence and mortality of comorbidities in India among confirmed COVID-19 cases

Figure 9 shows the prevalence and mortality of comorbidities in Bangladesh among confirmed COVID-19 cases. The most prevalent comorbidity in Bangladesh among the overall population was found to be diabetes followed by hypertension. Mortality rates were highest among the diabetic patients followed by cardiovascular disease patients. The least prevalent comorbid condition was hypo/hyperthyroidism. For Bangladesh, mortality was not reported in association with obesity and hypo/hyperthyroidism.

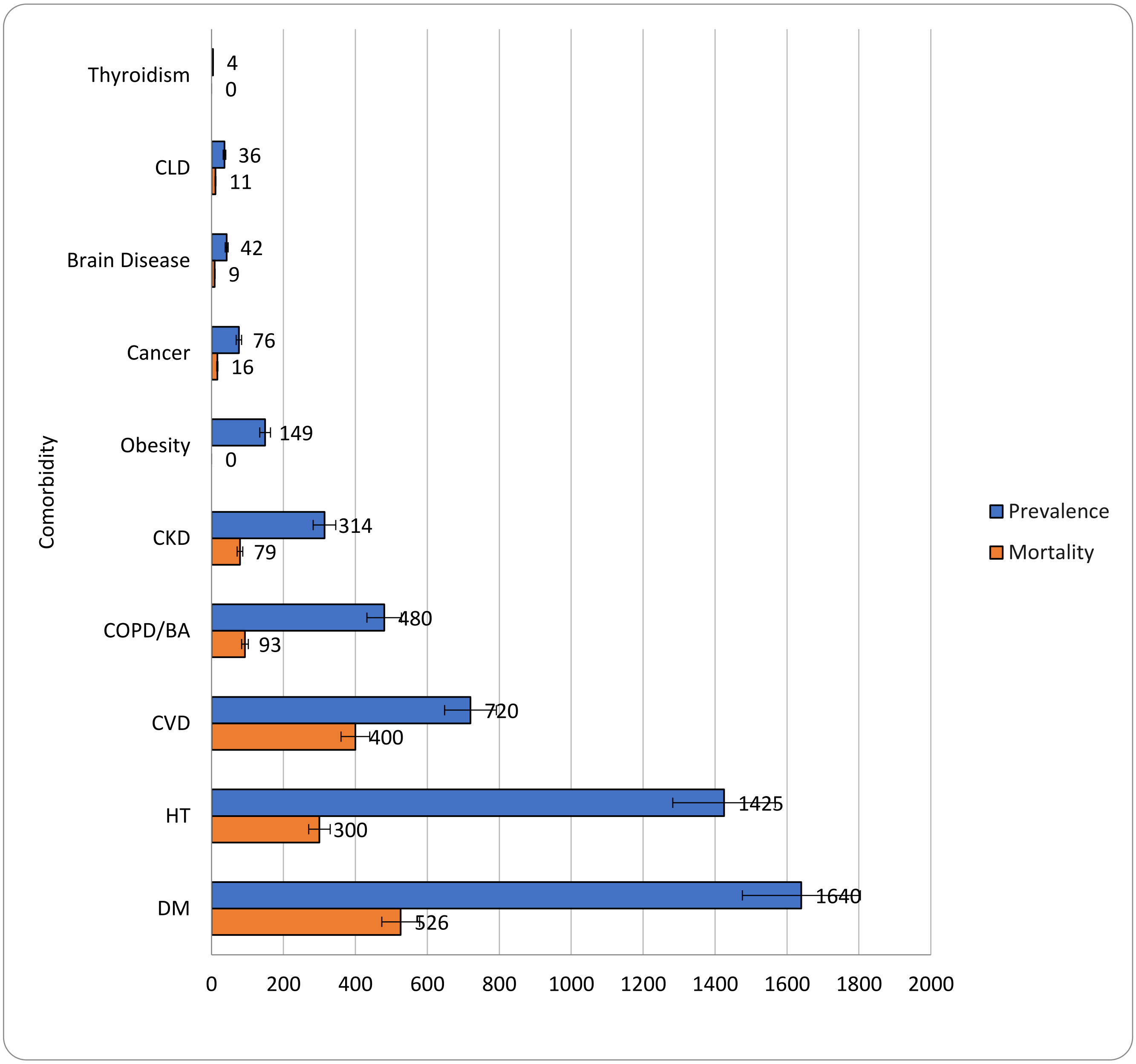

Fig 9: Prevalence and mortality of comorbidities in Bangladesh among confirmed COVID-19 cases

Figure 10 shows the prevalence and mortality of comorbidities in Pakistan among confirmed COVID-19 cases. The most prevalent comorbidity in Pakistan was found to be hypertension followed by diabetes - in both survived and non-survived population. The least prevalent comorbid condition was obesity. None of the selected studies from Pakistan reported the presence of hypo/hyperthyroidism.

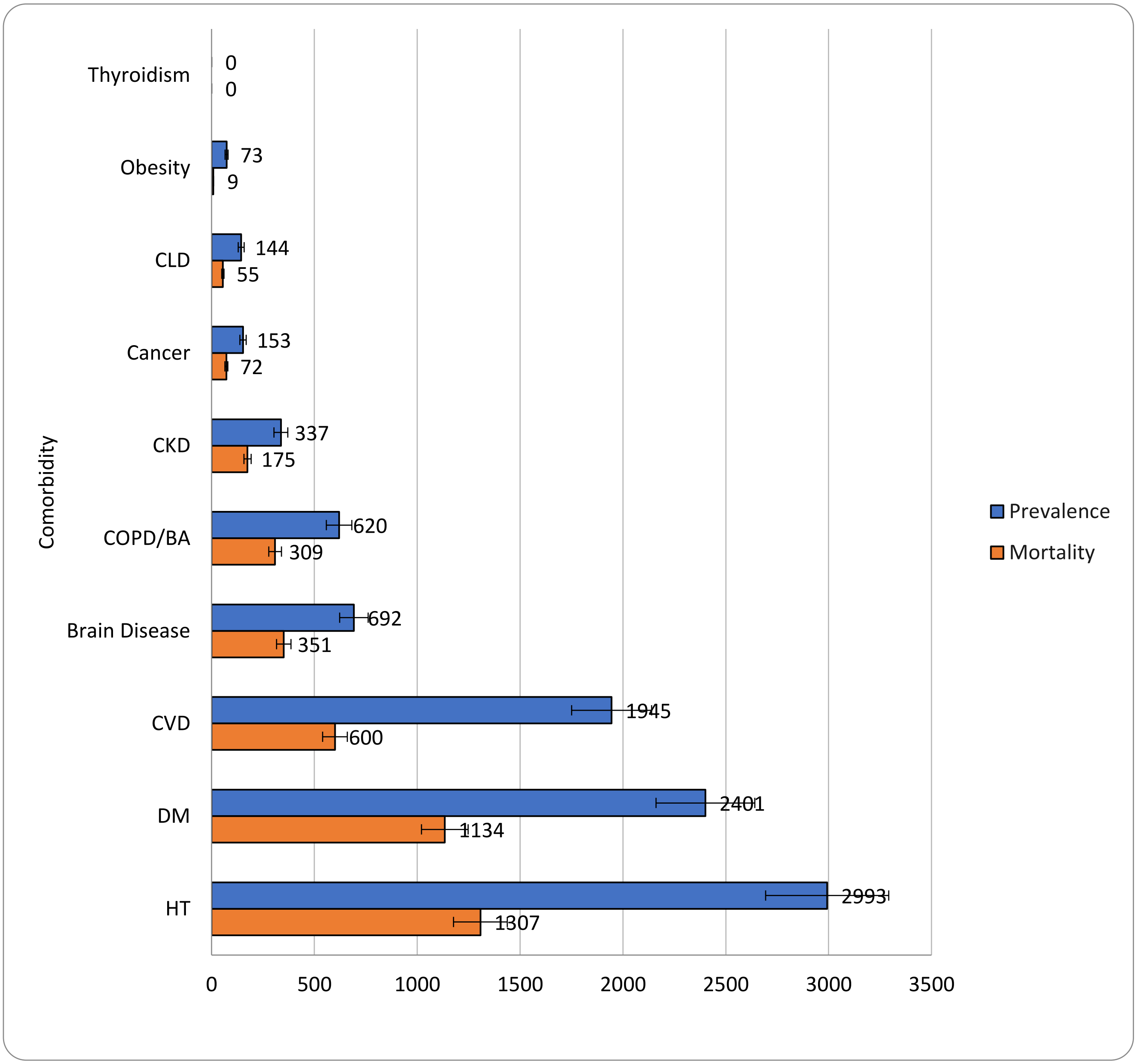

Fig 10: Prevalence and mortality of comorbidities in Pakistan among confirmed COVID-19 cases

Mortality analysis of COVID-19 comorbid patients in Bangladesh, India and Pakistan

According to Thakur et al. [25], the most prevalent comorbidity worldwide was hypertension followed by obesity, diabetes and cardiovascular diseases. Compared to the comorbid conditions reported worldwide, South Asia rarely reported obesity.

This data can be verified by figure 4, which shows the biweekly confirmed COVID-19 deaths in South Asia between March 2020 till December 2022.

- Diabetes

The mortality rate among COVID-19 patients with diabetes has been found to be particularly high in the South Asian countries of Bangladesh, India and Pakistan. An analysis of available data indicates that the mortality rate among COVID-19 patients with diabetes in Bangladesh is 61.23%, in India it is 49.25% and in Pakistan it is 55.26% (figure 11). These figures highlight the significant impact that diabetes has as a comorbidity on the outcome of COVID-19 infection in these countries. For all three countries, the mortality rate in diabetic patients is relatively high and suggests that diabetes is a significant risk factor for severe illness and death from COVID-19.

Diabetes is the most common comorbidity reported according to this study and it increases the risk of life-threatening COVID-19 infections. Most of the literature reviewed in this study had the same conclusion, where the death rate among all hospitalized patients was much higher in diabetic patients compared to non-diabetic patients [26; 27]. This risk increased many folds when cardiovascular disease and diabetes coexisted together in patients [28]. The South Asian population has a genetic resistance to insulin which increases the chances of developing Type II Diabetes Mellitus [29]. Furthermore, Saha et al. [17] reported that COVID-19 infected diabetic patients who required insulin had a greater risk of an unfavorable disease outcome and shorter survival time than the non-insulin required group. This proved to be a double edged sword as the frequency of patients who required insulin increased during infection with COVID-19 [30].

- Hypertension

An analysis of the available data indicates that the mortality rate among COVID-19 patients with hypertension in Bangladesh is 34.92%, in India it is 45.03% and in Pakistan it is 63.69% (figure 11).

These figures reveal the substantial impact of hypertension as a comorbidity on the outcome of COVID-19 infection in these countries.

Pakistan had the highest rate of mortality resulting from hypertension compared to India and Bangladesh. According to a study published in the Journal of the College of Physicians and Surgeons Pakistan, hypertension is one of the most common non-communicable diseases in Pakistan, with an estimated prevalence of 20-30% [36]. This means that more people in Pakistan are at risk of hypertension compared to Bangladesh and India, which could contribute to the higher mortality rate among COVID-19 patients with hypertension in Pakistan.

Hypertension is widely recognized to be associated with the severity of COVID-19 outcome and was seen as a frequent comorbid illness among the critical COVID-19 patients [31]. The observational and retrospective studies conducted in these regions of South Asia reported a high prevalence of hypertension among the patients. They also found that a higher proportion of hypertensive patients infected with COVID-19 were admitted to the ICU compared to patients with normal blood pressure [32]. Soumya et al. [33] reported that hypertension can be linked with up to 2.5 times more significant risk of lethal COVID-19, especially in an elderly population. Furthermore, in PLHIV patients infected with SARS-CoV-2, hypertension was significantly associated with mortality [34].

It has been established that non-communicable diseases such as hypertension and diabetes increase with age and this could be the reason for higher COVID-19 related deaths as observed in the present study. Due to the food habits of the South Asian population, these countries are normally prone to heart failure and hypertension [29].

- Cardiovascular diseases

An analysis of the available data indicates that the mortality rate among COVID-19 patients with cardiovascular diseases in Bangladesh is 46.57%, in India it is 11.42%, and in Pakistan it is 29.24% (figure 11). These figures reveal the substantial impact of cardiovascular diseases as a comorbidity on the outcome of COVID-19 infection in these countries.

One potential explanation for the higher mortality rate of cardiovascular diseases among COVID-19 patients in Bangladesh compared to India and Pakistan could be the differences in the healthcare infrastructure and resources available in these countries. Bangladesh and Pakistan might not have the same level of resources and facilities as India to manage the cases of COVID-19 with comorbidities such as cardiovascular disease. Additionally, the prevalence of cardiovascular disease might be higher in Bangladesh than in India and Pakistan, which could also contribute to the higher mortality rate.

In Bangladesh, the greatest risk factor for mortality among COVID-19 patients was seen in comorbid patients suffering from both diabetes and cardiovascular disease [28]. In patients with complications such as acute cardiac injury, a worse disease prognosis was expected [37]. Even though COVID-19 is primarily a respiratory illness, a high proportion of patients have been reported to develop new-onset cardiac dysfunction during the COVID-19 infection [38]. Gupta et al. [39] predicted a steep rise in cases of cardiovascular diseases among the asymptomatic population infected with SARS-CoV-2 in South Asian countries.

- Chronic Kidney Diseases

An analysis of the available data indicates that the mortality rate among COVID-19 patients with CKD in Bangladesh is 9.20%, in India it is 19.84%, and in Pakistan it is 8.53% (figure 11). It's worth noting that, compared to hypertension and diabetes, the mortality rate of COVID-19 patients with CKD is relatively low, however, it is still a significant comorbidity that needs to be considered in the management of COVID-19 patients.

The demographic characteristics of CKD patients showed a predominantly elderly population, suffering from more than one comorbidity [40; 41]. Younger patients suffering from COVID-19 and CKD did not succumb to the disease in most cases. Sindhu et al. [42] and many other studies reported a high mortality rate in patients with acute kidney injury, who needed ICU care and dialysis in India. Furthermore, the mortality rate increased with the frequency of dialysis requirement and among those getting dialysis through the central venous catheter versus those with an arteriovenous fistula. One study reported that the frequency of AKI in CODID-19 patients was around 25% among critically ill patients with preexisting comorbidities [43].

- Chronic Obstructive Pulmonary Diseases

COPD or chronic obstructive pulmonary disease refers to a group of chronic lung diseases that includes emphysema, chronic bronchitis and asthma [44]. An analysis of the available data indicates that the mortality rate among COVID-19 patients with COPD in Bangladesh is 10.83%, in India it is 3.39%, and in Pakistan it is 15.06% (figure 11).

As SARS-CoV-2 predominantly is a respiratory disorder, asthma patients were categorized as a high risk group for severe to critical COVID-19 infections. Qamar et al. [45] reported that patients with asthma had a higher chance to experience residual myalgia and dyspnea. The US CDC listed asthma as one of the risk factors of severe COVID-19 disease as various respiratory viruses were shown to solicit severe symptoms in people suffering from COPD. However, asthma was not prioritized as a risk factor in China [46]. This proved to be true for the South Asian population as well as the COPD patients with COVID-19 did not generally have a worse disease outcome.

- Cancer

The data provided shows that the mortality rate among COVID-19 patients with cancer in Bangladesh is 1.86%, in India it is 3.18%, and in Pakistan it is 3.51% (figure 11). It is important to note that cancer patients are more susceptible to severe infections and have a higher risk of mortality due to their compromised immune system. Additionally, cancer treatments such as chemotherapy and radiation therapy may also make cancer patients more vulnerable to COVID-19.

In cancer patients with COVID-19, mortality was seen to be determined by age, advanced stage of the disease and palliative intent of cancer treatment [35]. To compare between the various forms of cancer, lung cancer was prevalent among COVID-19 patients but breast cancer patients reported a lower mortality [47; 48]. Cancer patients with COVID-19 infection have a poor disease outcome and performance as immunocompromised patients have a greater risk of infection. Anticancer treatments administered within a month before the onset of the SARS-CoV-2 infection did not have a considerable effect on mortality [49].

- Chronic Liver Diseases

The data provided shows that the mortality rate among COVID-19 patients with chronic liver diseases in Bangladesh is 1.28%, in India it is 1.27%, and in Pakistan it is 2.68% (figure 11). It is important to note that patients with chronic liver diseases such as cirrhosis or hepatitis are at higher risk of severe illness and complications from COVID-19. This is because the liver plays an important role in the body's immune response, and liver disease can affect the body's ability to fight off infections.

According to Krishnasamy et al. [50], patients with comorbidity and liver enzyme elevation had a higher chance of mortality than patients without. They also reported that males had a higher liver enzyme elevation than females. When the population demographic was 40 years and above, it increased the risk for severe disease, ICU admission and mortality. Liver dysfunction can be used as a forewarning for disease severity [51].

- Brain Diseases

The data provided shows that the mortality rate among COVID-19 patients with brain diseases in Bangladesh is 1.05%, in India it is 1.25%, and in Pakistan it is 17.11% (figure 11). These figures reveal the impact of brain diseases as a comorbidity on the outcome of COVID-19 infection in these South Asian countries. It is worth noting that the mortality rate of brain diseases among COVID-19 patients is relatively low compared to other comorbidities in India and Bangladesh, but much higher in Pakistan.

Brain diseases have been categorized as the presence of any type of nervous system disorders, as well as cerebrovascular accidents. Cerebrovascular accidents (CVA) or stroke is a condition that occurs when the blood supply to the brain is interrupted, leading to brain damage. People with CVA are at a higher risk of severe illness and complications from COVID-19, due to the fact that they may have underlying cardiovascular disease. Patients with COVID-19 who had strokes were more likely to be elderly and have hypertension, which puts them at a higher risk of disease severity [52].

Bangladesh and India also reported obesity as a risk factor for worse disease outcomes. Obese patients were 1.13 times more susceptible to get severe COVID-19 [53]. Communicable diseases such as HIV and tuberculosis also worsened the disease outcomes. In COVID-19 patients with HIV, most were seen to have pre-existing conditions such as diabetes and hypertension, which was already a risk factor for severe COVID-19 infection [34].

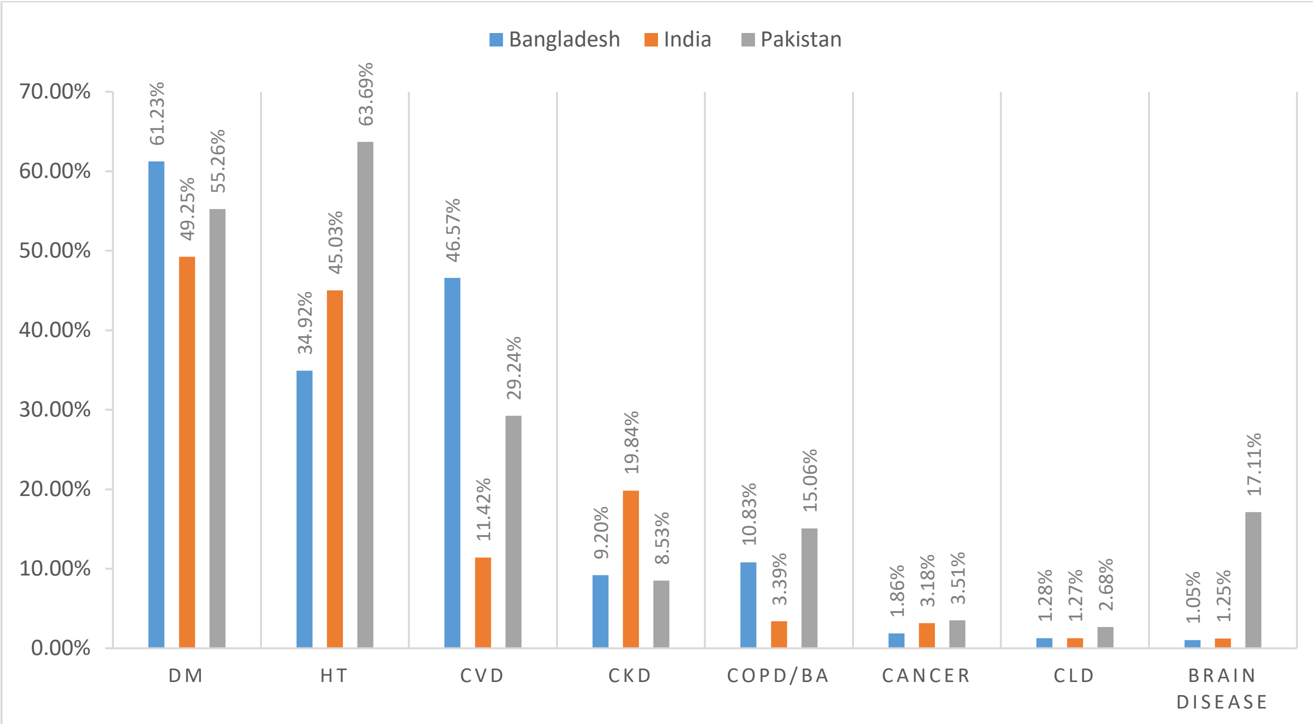

Figure 11: Mortality rates of COVID-19 comorbid patients in Bangladesh, India and Pakistan

Pooled prevalence of Diabetes, Hypertension and Heart Diseases

Diabetes, hypertension and heart diseases were observed as the most prevalent comorbidities among the South Asian population. Thus, forest plots representing the pooled prevalence of these three comorbid conditions were generated.

Figure 12 shows the forest plot representing the overall pooled prevalence of COVID-19 affected diabetic patients in South Asia. Out of the 91 studies, diabetes was reported in 85 studies conducted on the overall population and it was reported in 82 studies conducted on COVID-19 deceased population. Out of the 85 studies, 58 were conducted in India, 17 were conducted in Pakistan and 10 were conducted in Bangladesh. These studies together comprised of 15080 study participants who were diabetic and affected with COVID-19, while 4264 of these diabetic participants succumbed to COVID-19. Random effect meta-analysis showed that 33% of COVID-19 study participants were diabetic with high number of heterogeneity (I^2 = 98.33%, P < 0.0001). This indicates that the prevalence of diabetes among the COVID-19 affected population in South Asia was found to be high, with a high degree of variability across studies. The results of this analysis suggest that diabetes may play a significant role in the severity and outcomes of COVID-19 in South Asia.

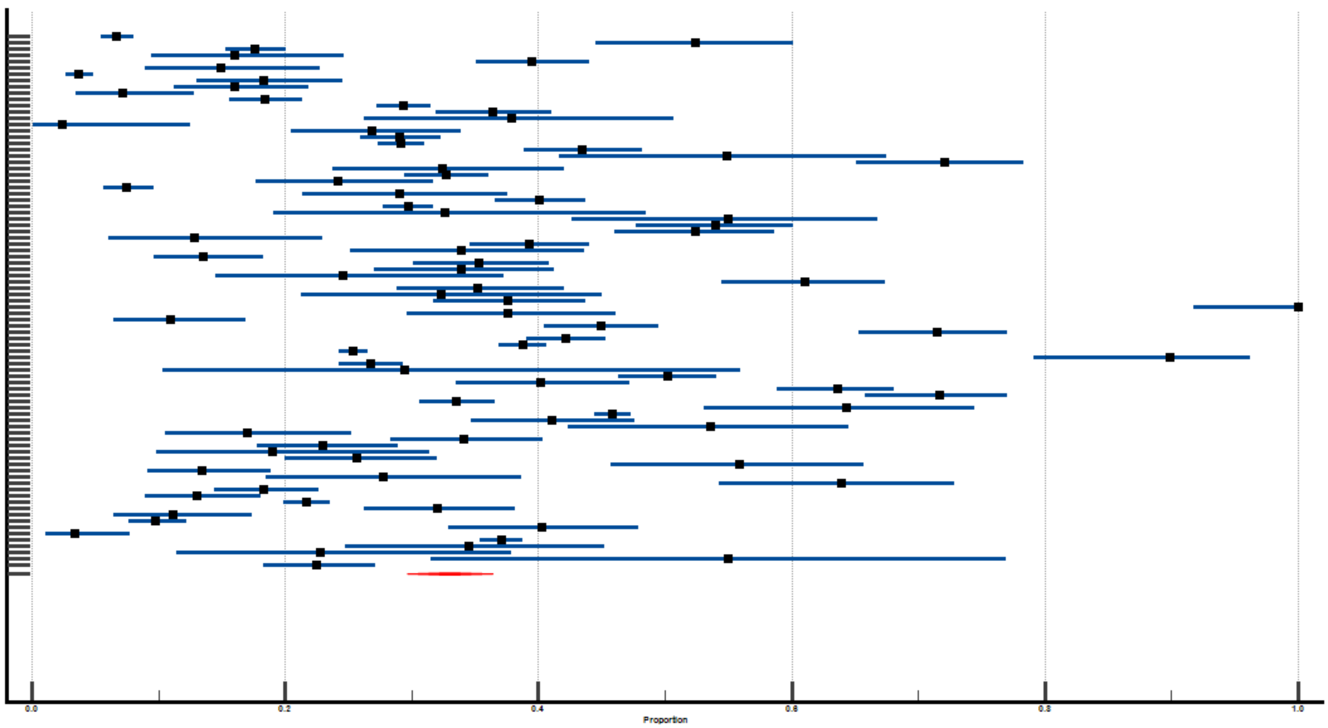

Figure 12: Forest plot representing overall pooled prevalence of COVID-19 affected diabetic patients

Figure 13 shows the forest plot representing the overall pooled prevalence of COVID-19 affected hypertensive patients in South Asia. Out of the 91 studies, hypertension was reported in 83 studies conducted on the overall population and it was reported in 78 studies conducted on COVID-19 deceased population. Out of the 83 studies, 58 were conducted in India, 16 were conducted in Pakistan and 9 were conducted in Bangladesh. These studies together comprised of 14860 study participants who were hypertensive and affected with COVID-19, while 3988 of these hypertensive participants succumbed to COVID-19. Random effect meta-analysis showed that 40% of COVID-19 study participants were hypertensive with high number of heterogeneity ($I^2 = 98.79\%$, $P < 0.0001$). This suggests that the prevalence of hypertension in the COVID-19 affected population in South Asia may vary significantly across different studies and geographic locations.

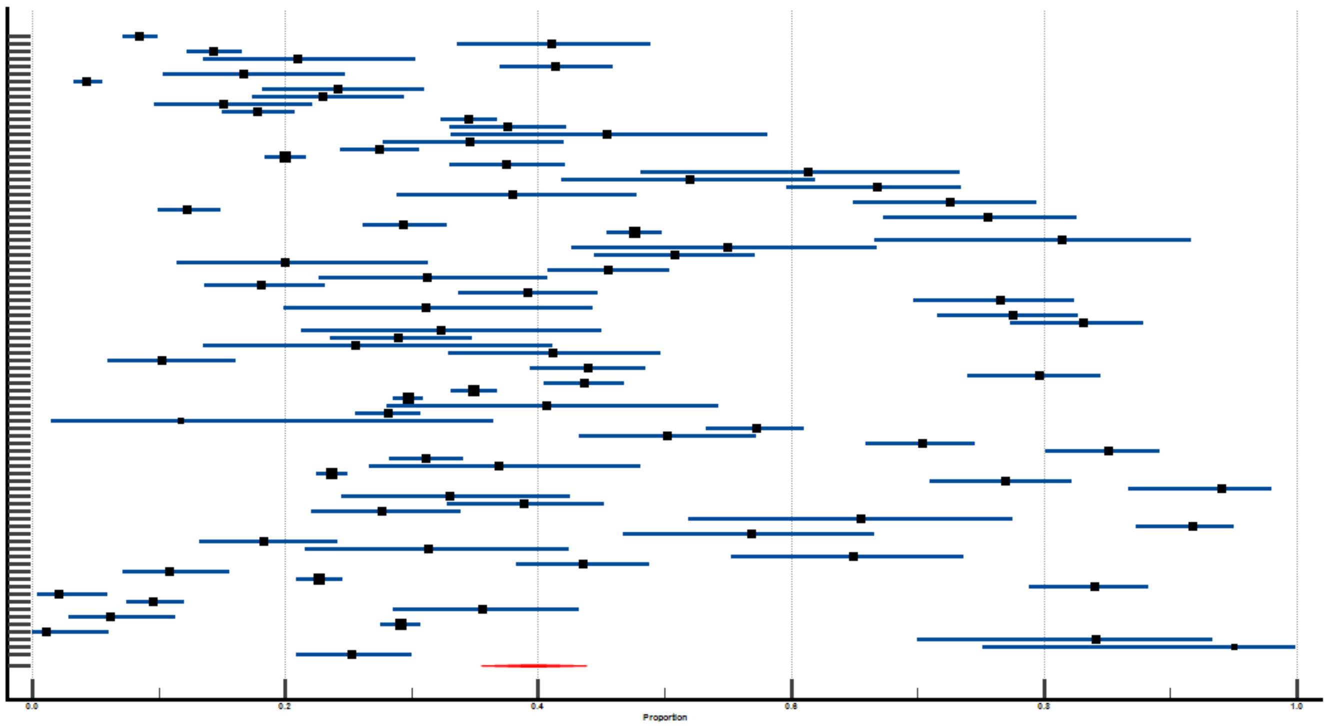

Figure 13: Forest plot representing overall pooled prevalence of COVID-19 affected hypertensive patients

Figure 14 shows the forest plot representing the overall pooled prevalence of COVID-19 affected heart disease patients in South Asia. Out of the 91 studies, heart disease was reported in 81 studies conducted on the overall population and it was reported in 78 studies conducted on COVID-19 deceased population. Out of the 81 studies, 54 were conducted in India, 17 were conducted in Pakistan and 10 were conducted in Bangladesh. These studies together comprised of 4770 study participants who had a history of heart diseases and affected with COVID-19, while 1604 of these heart disease participants succumbed to COVID-19. Random effect meta-analysis showed that 11% of COVID-19 study participants had heart disease with high number of heterogeneity (I^2 = 98.16%, P < 0.0001). This suggests that there is a large variation in the prevalence of heart disease among COVID-19 affected patients in different studies.

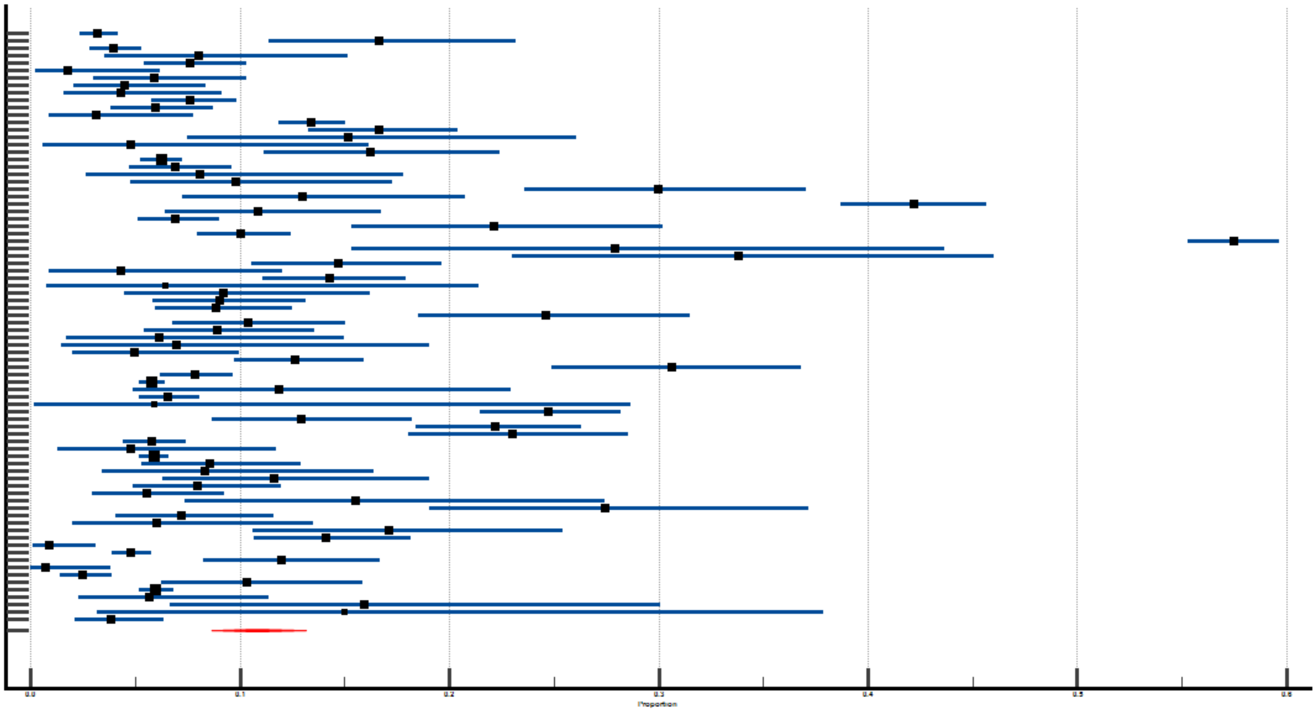

Figure 14: Forest plot representing overall pooled prevalence of COVID-19 affected heart disease patients

Discussion

In this systematic review, the purpose was to elucidate comorbidities associated with COVID-19 disease and more specifically among the fatal cases. The review included 91 studies with 48,908 patients infected with COVID-19, a large proportion of inpatients with COVID-19 were found to have various coexisting comorbidities. Moreover, comorbidities and complications were strongly associated with a higher risk of severe and critical outcomes, worsening illness, ICU admissions as well as mortality during centralized isolation and hospitalization. The most common symptoms reported in these studies were fever, cough, dry cough, fatigue, dyspnea, anorexia, myalgia, headache and breathing difficulties. In the 91 selected studies, the ratio of infection was reported higher in males than in females and the disease burden fell on the elderly population- those above 50 years of age. This result is consistent with the studies conducted worldwide.

The most prevalent comorbidities were diabetes, heart disease and hypertension in mild, moderate, severe and critical patients, and ultimately also lead to a higher prevalence in the deceased population as well. The results were in accordance with findings from previous reviews that patients with COVID-19 have a highly estimated prevalence of coexisting cardiovascular diseases, hypertension and diabetes. In addition to summarizing various comorbidities of COVID-19, we explored the mortality due to complications related to the presence of these disorders that are highly associated with COVID-19. Some studies with small sample sizes reported stroke, chronic liver diseases, obesity, hypo/hyperthyroidism and nervous system disorders. This finding suggested that most of these diseases can increase the risk of death in these patients than in those without these comorbidities.

For all three comorbidities of diabetes, hypertension and heart diseases, we observed a high level of heterogeneity among the studies included in the analysis, meaning that the estimates of comorbidity prevalence among the COVID-19 affected population varied greatly across the studies. This may be due to differences in study populations, study design, data collection methods, and other factors. The high prevalence of these comorbidities among COVID-19 affected individuals in South Asia highlights the need for targeted interventions and improved management of this comorbidity in the region to improve COVID-19 outcomes.

Over the course of the pandemic, several researches have been conducted to investigate the mechanisms that can explain the adverse outcomes of COVID-19 infection in patients with comorbidities. The undesirable disease outcome of COVID-19 diabetic patients is a result of their weakened immune system, specifically their innate immunity. Innate immunity can be affected temporarily by transient hyperglycemia in response to the SARS-CoV-2 infection. Immune dysfunction of diabetic patients is multi-faceted - hyperglycemia, inhibition of neutrophil chemotaxis, altered production of cytokine, ineffective microbial clearance, impaired T cell-mediated immune response, use of renin-angiotensin-aldosterone system antagonists and phagocytic cell dysfunction contribute to the immune dysfunction in this group [54]. The reduced expression of ACE2 is responsible for playing a major role in the disease severity of diabetic patients [55]. Different markers such as interleukin (IL)-1, IL-6, C-reactive protein, and D-dimer have been linked with the severity of the disease among the diabetic population. Elevated levels of cytokines, specifically interleukin-6 and tumor necrosis factor-α (TNF-α), have been proposed to explain the disease prognosis among COVID-19 hypertensive patients as well. Hypertension is also associated with endothelial dysfunction, RAS imbalance and a pro-inflammatory state [32]. The traditional RAS axis activation along with the unconventional RAS axis down-regulation has been theorized to be the fundamental factors contributing to severe disease outcomes in COVID-19 patients. Moreover, Kamyshnyi et al. [56] pointed out another mechanism connecting arterial hypertension and COVID-19 - the dysregulation of the immune system leading to a cytokine storm, facilitated by an imbalanced response of T helper cell subtypes. COVID-19 patients with cardiovascular diseases are also vulnerable to the cytokine storm occurring in response to the systemic inflammation [57]. Severe viral illness puts an extra demand on the heart and the increased heart rate coupled with low oxygen levels due to respiratory symptoms, myocarditis and increased propensity for blood clot formation can lead to a heart attack or develop congestive heart failure. Furthermore, myocarditis has also been observed in COVID-19 patients. The myocardial tissue expresses ACE2 receptors, thus allowing the virus to enter into the heart and cause damage to the myocardial tissue. This leads to the death of the tissue and also death in severe cases [35]. In COVID-19 patients with cardiovascular diseases, Liaqat et al. [58] reported in their study that half the study population presented with new electrocardiographic changes and ST depression. In severe conditions, abnormal echocardiography findings with right ventricular dilation and dysfunction. Among those who succumbed to the disease, they all had abnormal Echo and ECG findings with less than 60% ejection fraction. They also found a positive correlation between COVID-19 fatality and markedly elevated troponin levels and ECG abnormalities.

It has been hypothesized that the co-expression of ACE2 and TMPRSS, both of which are highly expressed in kidneys, lead to a conducive condition for the entry and localization of the virus. This means that patients with CKD have an increased risk of severe COVID-19 infections. Coupled with the over-expression of the aforementioned genes, Ramamurthy et al. [59] also attributed reduced immune response, chronic inflammation, elevated oxidative stress, uremia, and endothelial dysfunction to the disease severity. Chronic kidney diseases also coexist with diabetes and cardiovascular diseases, which are known to cause a worse disease outcome. Similar contributors were reported in patients with liver diseases. Vadiraj et al. [60] proposed that the immune-mediated inflammatory response, hepatic congestion, systemic hypoxemia, direct infection of hepatocyte, cytokine release, ischemic hepatitis and venous and arterial thrombosis could be a likely cause for the disease severity in COVID-19 patients with chronic liver diseases. Once again, the correlation of ACE2 expression in the gastrointestinal tract, vascular endothelium and cholangiocytes of the liver lead to a favorable entry of the virus.

Mechanisms involved in the increased susceptibility of chronic obstructive pulmonary diseases are increased expression of ACE2 in the lung epithelium, reduced antiviral defense and dysfunctional immunity. Blocking of the renin-angiotensin pathway promotes pathogenesis of the disease, induces pulmonary edema and impairs lung function [33]. Most COPD patients also have a history of smoking and have been exposed to noxious gasses or pollutants capable of changing pulmonary defenses over time. As a consequence, patients with COPD are more susceptible to viral respiratory infections such as SARS-CoV-2, and this is aggravated by bacterial co-infections leading to a worse disease prognosis [61]. Wardana et al. [46] reported that the symptoms of COVID-19 and asthma are very similar, except for the presentation of fever in COVID-19 infections. Children with asthma have also been reported to be at a greater risk of developing pneumonia and acute respiratory disease in the same study, which can trigger an exacerbation of asthma.

Due to the diverse character of cancer types, heterogeneous malignancy-related mutations and mechanisms, it has been hard to suggest a general mechanism responsible for higher vulnerability among COVID-19 infected cancer patients. Multiple studies [62; 63; 64] have linked CXCL10, NRP1 and ACE2, along with their co-expressed genes, to the binding activity and immune responses in case of malignancy and COVID-19. Samad et al. [63] concluded that the high expression of ACE2 can be a possible reason for the increased susceptibility of lung cancer patients towards COVID-19, while Balaji et al. [65] proposed that the increased protease levels in chronic periodontitis and oral cancer can lead to a greater risk of oral mucosa mediated SARS-Cov-2 infection. Along with ACE2, NRP1's upregulation was identified in renal carcinomas [64]. This can be used to explain the high mortality of COVID-19 patients suffering from kidney cancers. Biological markers such as leukocytosis, lymphopenia, elevated levels of C-reactive protein (CRP), procalcitonin (PCT), D-dimer, IL-6 (Interleukin-6), Neutrophil to

Lymphocyte ratio (NLR), and Lactate dehydrogenase (LDH) have all been observed in COVID-19-infected cancer patient [47].

COVID-19 related fatalities have shown a much lower rate in South Asia, compared to countries like the US, UK, Brazil, Mexico and South Africa. Despite being a densely populated region, they were able to avoid a disastrous mortality rate and this can be due to a combination of factors. Firstly, the pandemic arrived in South Asia much later compared with other countries, which gave them a head-start to plan ahead and take preventive measures. Another concerning factor was that in these countries, deaths were not reported promptly, which may have resulted in an underestimated mortality rate. There have been hypotheses implicating the genetic advantage for South Asians [66]. Furthermore, the burden of non-communicable diseases falls in developed countries to a greater extent than in South Asia because of more urbanized states and food habits [67].

Age and gender has been reported as a risk factor in many studies. Rana et al. [68] reported that individuals in the 0-50 age group and the female gender were less prone to developing a severe condition that would lead to their death. Age and gender also played a major role in explaining the death rates of South Asia. As per the WHO report on COVID-19 in Bangladesh, till August 30, 2021 [69], the male showed higher confirmed (67%) and death (65%) cases compared to female (33% and 35%, respectively), the case fatality ratio (CFR) for males was higher than females. However, compared to the other countries, Bangladesh had a relatively lower mortality rate and a possible reason for this could be the population demographics, where only 10-15% of the population is over 50 years [30]. One study noted that in Bangladesh and Pakistan, the male population are more involved in outdoor activities and have to communicate with almost every class of people, making them more susceptible to contracting the infection than the female population [70]. The same study also pointed out that females have a relatively higher innate and adaptive immunity due to a high density of immune related genes in the X chromosome. SARS-CoV-2 viruses use SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) to enter the host cell and ACE2 is more prevalent in men than women. Soumya et al. [33] reported that in two independent groups of patients with heart diseases, the concentration of ACE2 in plasma was greater in men than in women. The South Asian countries also have a higher rate of smoking in men than women, making them a greater target for contracting the disease.

People above the age of 50 were highlighted to be more prone to disease severity on account of a weakened immune system and a weak cardiovascular function. Moreover, diabetes and hyperlipidemia, which are conventional risk factors of cardiovascular ailments, can also bring about an adverse effect in immune functions. Comorbidities are widespread among this age group, like diabetes, high pressure, low lungs and kidney function and other chronic diseases [70]. In patients with hypertension and cardiovascular diseases, the increased expression of ACE2 is likely to increase the susceptibility of SARS-CoV-2. In terms of population demographics, these countries have a lower elderly population compared to developed countries and most of the elderly people were quarantined in their houses. This led to a lower CFR among the elderly population in South Asia.

In Pakistan, higher fatality was seen in more populated cities such as Karachi, Lahore and Islamabad and Bangladesh had a higher fatality in Dhaka. Due to the presence of many rural regions and smaller urban centers in South Asia, where the population density is low, the population could avoid contracting the disease to a certain extent. At the same time, in a study conducted by Sharma et al. [71], lower socio-economic status population in India has exhibited a notably greater mortality from COVID-19. This was explained by the low education status among these individuals, who had a low health literacy due to a lack of understanding of public health preventive measures and thus, delayed seeking healthcare in due time. Prevalence of smoking, poor nutrition and comorbidities were also high among this group. Therefore, they had suffered from a more severe disease at presentation to hospital and required a greater need for oxygen and ventilator support.

Due to a combination of the factors discussed above, a high percentage of the population in South Asia were asymptomatic to the disease during the first wave in 2020. In Sri Lanka, the low mortality rate was attributed to a majority of mild or asymptomatic illness despite having comorbidities [72]. Nazneen et al. [73] reported in a study conducted among 44865 individuals between April and October 2020 that 87% of the SARS-CoV-2-positive individuals were asymptomatic. Similar findings were reported by the Indian health ministry in 2020. One of the leading newspapers in Nepal found that almost 99% of the COVID-19 cases in Nepal were asymptomatic and among those infected, 97% of the cases came from other countries. These asymptomatic cases led to a spike in the infection rates but not the mortality rates.

COVID-19 struck the world in "waves". The first wave occurred in 2020, leading the way for the second, more disastrous wave, in terms of mortality, in 2021. According to UNICEF, the South Asian region alone accounted for 4,903 deaths on 18 May, 2021. Among these 4903 deaths, India accounted for over 92% of the fatalities, which has been the highest number of deaths ever recorded in a single country since the beginning of the pandemic (Figure 4). Bangladesh and Pakistan also faced similar devastating surges during the second wave. In the first wave, as well as the second wave, India had the highest number of deaths among the selected countries. India was most vulnerable to COVID-19 deaths in the summer of 2021 and this can be attributed to the emergence and spread of the delta variant (B 1.617.2). This variant proved to be deadlier than the alpha variant (B 1.1.7) since many people faced worse disease outcomes as it became evident that despite seropositivity at a population level, our immune system was unable to eliminate the virus [77]. This variant took a toll in the Bangladesh population in September 2021, when the mortality was the highest ever recorded (Figure 3). In Bangladesh, people under 41 years of age were testing positive for COVID-19 in a greater frequency during the second wave of the pandemic. In a study conducted among kidney transplant recipients in a large transplant center in India, it was seen that older age and obesity showed a greater association with mortality during the first wave [79]. Moreover, the presence of multiple comorbidities and chest imaging changes were also associated with a higher fatality during the first wave.

Variations in sample size, severity of illness, age distribution, sex distribution, and the presence of comorbidities are the factors that cause differences in mortality rates in existing literature. As comorbidity data collection for COVID-19 was not collected for all diagnosed cases, the contribution of comorbidities to fatal outcomes could not be inferred accurately. However, the comorbidity data that was collected for COVID-19 mortality surveillance pointed towards clinical and epidemiological attributes of fatal cases. Missing data such as this could be due to breaking of the chain of communication from the notification of death to the publication of press releases, failure to upload press releases, or lack of information about people who have died.

Enough data about the Sri Lankan and Nepalese population could not be obtained as these countries did not have enough published literature regarding COVID-19 infection and comorbidities. This disparity in the data available does not point to a precise scenario of the effect of comorbidities in the South Asian population.

Another point of concern in this study is the possibility of data duplication. It is possible that two different studies by different authors could have included the same population if it was published in the same region, which, once again, would lead to an inaccurate representation of comorbid conditions and COVID-19.

The mechanisms discussed in this review are subject to further evaluation and study, as this is a novel virus that has not been studied in great depth yet. Further clinical and laboratory studies should help to form stronger conclusions about the potential mechanisms of SARS-CoV-2 infections and comorbid conditions. This, in turn, will aid in developing a better understanding of the effects of the virus to formulate appropriate treatment plans.

Additionally, the healthcare infrastructure and resources available in these countries must be taken into account when evaluating the impact of comorbidities on the outcome of COVID-19 infection. Factors such as access to healthcare, socioeconomic status, and demographic factors may also play a role in the mortality rate among COVID-19 patients with comorbidities in these countries.

Conclusion

As such, it is crucial for public health officials to take the presence of comorbidities into account when developing strategies to combat COVID-19. This includes targeted vaccination and education efforts, as well as increased access to medical care for individuals with comorbidities. Additionally, further research is needed to better understand the mechanisms by which comorbidities increase susceptibility to COVID-19, as well as to develop more effective treatments for individuals with comorbidities who become infected with the virus.

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