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A REVIEW ON THE PREVALENCE, SEVERITY AND TREATMENT OF DIABETES MELLITUS IN COVID-19 PATIENTS

S.Vedhapal Jeyamani[1], K. Karthickeyan[2]

[1]Department of Pharmacy Practice, K.K.College of Pharmacy, Gerugambakkam, Chennai, India
[2]Professor and Head, Department of Pharmacy practice, School of Pharmaceutical sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai, India

Corresponding Author: swetha21112000@gmail.com

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ABSTRACT

The objectives of the review was to summarize the comorbidities of patients with COVID-19 and to find out potential factors associated with severe disease, and to describe the treatment summary of Diabetes mellitus in COVID-19 along with describing the severity by comparing the ICU admission and mortality. For reporting systematic review and results, the study had followed PRISMA guidelines which searched pub med, Google scholars to find relevant articles using keywords "COVID-19", "SARS-CoV2" and Diabetes mellitus. Articles were selected between the period of 3 years (from 2019 to 2021). Extracted data were entered into Microsoft excel and were restrained which includes study designs (e.g., date of conduct, sample size), patient characteristics, study methodology (e.g., eligibility criteria, method of randomization, and blinding), intervention and main results. Characteristics of each patient data was collected on excel sheet and interpreted on various end points and outcomes. Among 13 studies, 5297 patients had Diabetes mellitus as major comorbidity of which male (57.1%) and female were 42.9%. The prevalence of comorbidities varies from (1-12.6%) for smokers, (8 to 41.6%) for HTN, (7.4 to 70.8%) for DM, (1.6 to 23.0%) for CVD, (0.7 to 2.9%) for CKD, (0.5 to 4.6%) for CLD. By comparing the ICU admission patients of COVID-19 with DM without DM, it shows that Covid-19 patients with Diabetes mellitus had more risk of ICU admission (36.8%). In prevalence of survivors versus non-survivors in COVID-19 patients with Diabetes, the survivor rate (62.2%) is higher than non-survivors (13.4%) which illustrate that COVID-19 with Diabetes have less mortality rate. Initial studies found that the male patients had Diabetes mellitus as major comorbidity in COVID-19 when compared to females. The studies of prevalence of comorbidities in COVID-19 shows high prevalence of Diabetes makes it as a major comorbidity in patients with COVID-19. And by comparing the ICU admission patients of COVID-19 with Diabetes and without Diabetes, studies show that COVID-19 associated Diabetes patients have more risk of ICU admission. Then comparing the prevalence of survivors versus non-survivors shows that the COVID-19 patients with Diabetes also have less mortality rate.

KEYWORDS: COVID-19, Diabetes mellitus, Comorbidity, multi-factorial, Systematic review

INTRODUCTION

COVID-19:

The novel Coronaviruses (nCoV) belong to the viruses that cause illnesses such as the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). It is known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and caused the pandemic disease called coronavirus disease 2019 (COVID-19)[1]. Individuals who contract the virus may experience respiratory symptoms that range from mild to moderate and may recover without needing any special medical attention. However, some may become critically ill and require medical care. Those who are advanced in age or have pre-existing medical conditions such as cardiovascular disease, Diabetes, chronic respiratory disease, or cancer are at a higher risk of developing severe illness. The pandemic had caused significant harm to global demographics, resulting in over 5.3 million deaths worldwide[2]. This crisis is now considered to be the most significant global health emergency since the influenza pandemic of 1918[3]. The clinical manifestations of this particular virus have exhibited deleterious impacts on systems other than the respiratory system (primary target organ) e.g., brain, haematological system, liver, kidneys, endocrine system. Coronaviruses (CoV) are enveloped single-stranded RNA virus. Therefore, it is crucial that the COVID-19 approach emphasizes hospital care while undervaluing the role primary care plays in ensuring continuity of care[4]. Novel coronavirus pneumonia (COVID-19) has a higher prevalence and lower mortality rate than Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Ever since the outbreak of coronavirus disease 2019 (COVID-19) due to a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of infected cases and associated mortalities due to COVID-19 were thriving. A significant association with worse outcomes were seen in People with these comorbidity[5].

PATHOPHYSIOLOGY

SARS-CoV2 has a diameter of 60nm to 140nm and has distinctive spikes ranging from 9nm to 112 nm. In which the distinctive spikes give the appearance of the solar corona[6]. The SARS-CoV2 presented with S-Spikes move towards living via windpipe and it gets enters into the alveoli, which is the structural and functional unit of lungs. In alveoli, the air sac structure is made of alveolar cell lining and this cell contains ACE-2 inhibitor. After the enter with the help of S-spike which binds to ACE-2 inhibitor a usual process takes place during this stage called endocytosis direct fusion, in this process cell goes through encoding in the cytoplasm and then it gets attached to host ribosome to produce protein containing RNA polymerase[7]. Positive standard and Negative standard take place in each step with the help of endoplasmic reticulum, then it reaches the Golgi apparatus to be covered by new progenitor virus which knows the act of the alveolar cell by exocytosis after that a new progenitor virus formed which trigger an inflammatory response which induces the production of interface and cytokines. Followed by this production, stimulation occurs to release alveolar macrophages. Alveolar macrophages give rise to TNF-alpha I, IL, IL-6, IL-8 and chemokines (carrying fever) and produces damage to alveoli[8]. Symptoms appear after 2-14 days of invasion period of Coronavirus, in which the above chemical process and chemical substances increase the vascular permeability and adhesion molecule. It leads to leakage of fluid internally causing interstitial oedema leads to Dyspnoea and Hypoxemia[9].

DIABETES RELATION IN COVID 19

When someone gets infected with SARS-CoV2, it can cause the body to produce substances that cause inflammation. These substances include lipopolysaccharide, which is a molecule found on the surface of some bacteria, as well as cytokines, which are proteins that help

regulate the immune response. Modulation of natural killer cell activity (increased or decreased) and IFNγ production can increase the interstitial and/or vascular permeability for pro-inflammatory products. It causes increased reactive oxygen species (ROS) production. The aforementioned effects can result in several lung-related complications, including Acute respiratory distress syndrome (ARDS), Acute lung damage, and Lung fibrosis. ROS production and viral activation of the Renin–Angiotensin–Aldosterone system (RAAS) (via increased angiotensin II expression) cause insulin resistance, hyperglycaemia and vascular endothelial damage, all of which contribute to cardiovascular events, thromboembolism and disseminated intravascular coagulation (DIC) [10].

Infection also causes increases in the clotting components fibrinogen and D-dimer leading to increases in blood viscosity and vascular endothelial damage, and associated cardiovascular events, thromboembolism and DIC[11]. Evidence reported in the Journal of Diabetes and Centre for Disease Control and Prevention (CDC) showed Diabetes as the most important comorbidity associated with a 50% higher risk of fatal outcomes in COVID-19 cases with Diabetes than their non-diabetic counterparts[12]. Diabetes is considered as independent risk factor for complications and death during 2002 to 2003 outbreak of severe acute respiratory syndrome (SARS-CoV1). According to estimates, 463 million individuals worldwide were anticipated to have diabetes mellitus in 2019[13]. It is one of the most common chronic illnesses and can have fatal multisystemic complications. While the relationship between severe COVID-19 infection and diabetes mellitus has been documented in multiple investigations, it is still unknown if individuals with DM are more vulnerable to COVID-19. Given the significant incidence of diabetes, it's critical to comprehend the unique features of COVID-19 infection in Diabetic population[14].

METHODS

SOURCE OF DATA AND SEARCH STATEGY

The research complies with research and reviews along with the outcomes relevant publications have been identified by exploring PubMed and Google Scholar[15]. The search contains coupled medical subject categories and keywords for COVID-19 associated diabetes patients. The search policy adheres to the randomized clinical trial standard filter. The search phrases "2019 novel coronavirus and COVID-19" and "comorbidities, mortality, severity" with a language constraint of only English are indicated in the indices of the different databases. The review examined the complete texts of appropriate papers to determine eligibility after screening the article titles and abstracts for relevancy.

In order to find any further research that might be pertinent; the study looked through the bibliographies of the articles that satisfied the qualifying requirements. Independently, four reviewers collected potentially pertinent studies, assessed research eligibility, and conducted screening based on inclusion and exclusion criteria. Articles were chosen during a three-year period (2019 to 2021). Patients having a confirmed COVID-19 diagnosis, patients of all ages, and patients who had spent at least 15 days in the hospital were also included. Excluded were full text papers with insufficient data, patients without a verified COVID-19 diagnosis, pregnant and lactating women, non-English complete texts, and research on the western population. Following an initial electronic search of PubMed and Google Scholar, 48 articles were found in the records. The full text articles were then evaluated for eligibility, and after the titles and abstracts were screened, 30 articles were chosen. Of those, 17 articles were subsequently excluded due to various reasons, including insufficient data [6], non-English full text [5], and western population [6]. 13 studies were thus ultimately chosen for the investigation.

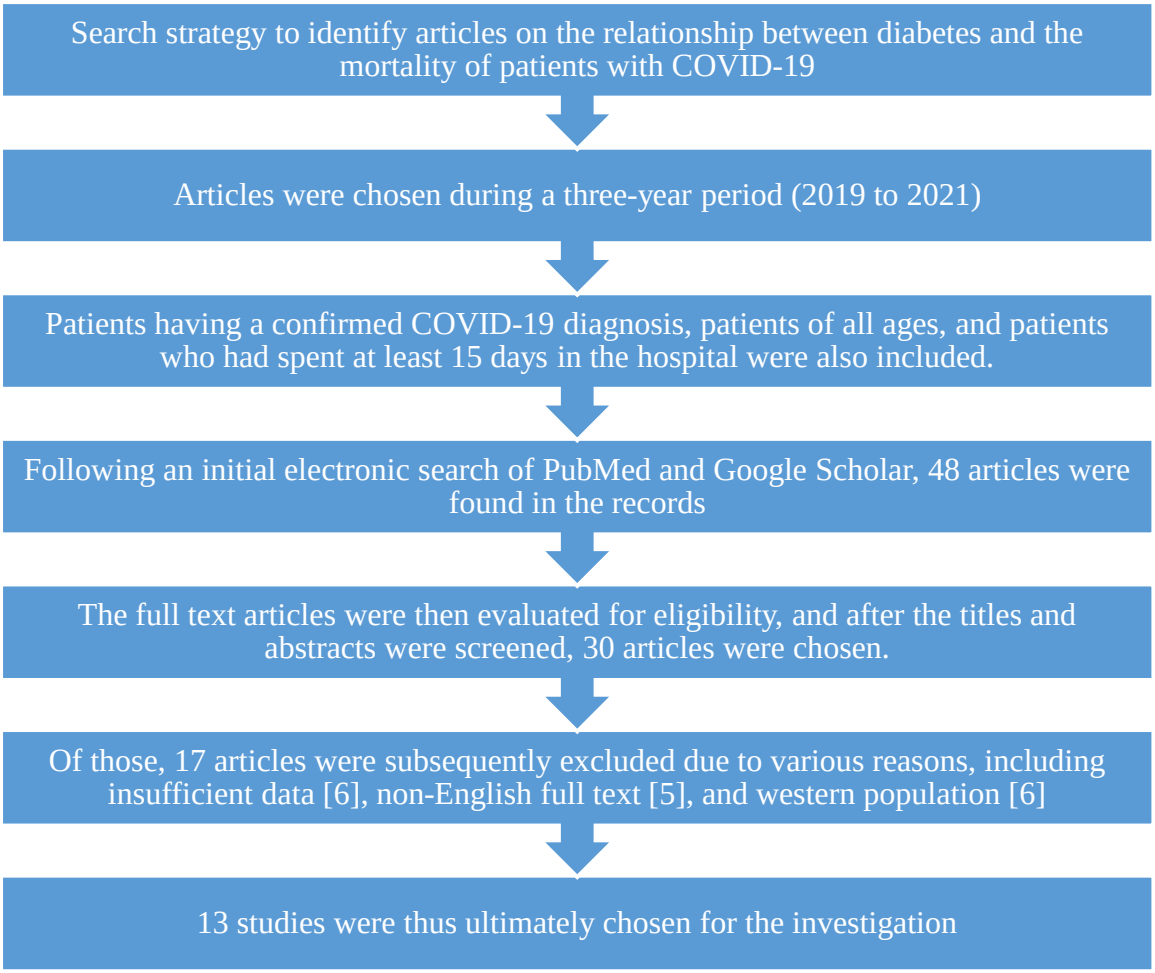

Fig 1: Flow diagram for literature search and study selection

DATA EXTRACTION

Data extraction and assessment were done and the extracted data were entered into Microsoft excel and were checked. Including study designs (e.g., date of conduct, sample size), patient characteristics, study methodology (e.g., eligibility criteria, method of randomization, and blinding), intervention and main results. Literature search was conducted in the electronic database of PubMed, Google Scholar, Elsevier from inception until august 31, 2021 using keyword “COVID-19”, “SARS-CoV2”, and Diabetes. Characteristics of each patient was collected on excel sheet and analysed on various end points and outcomes. The following data were extracted from full-text reports for further assessment: study characteristics, number of patients reported, patient characteristics and co-morbidities, present or prior history of COVID-19, the severity of Covid-19, the time from COVID-19 to Diabetes. Data on the following variables were extracted from each article. The extracted data was included individually on designed tabular columns.

DATA ANALYSIS

The statistical analysis was conducted using SPSS software to describe the characteristics of the study population. Continuous variables were reported using means and standard deviations, while categorical variables were reported using proportions. A test of proportions was conducted to compare risk factors and outcomes. Categorical variables were analysed using chi-squared or Fischer's exact test[16]. A p-value less than 0.05 were considered

statistically significant. Multivariate logistic regression was used to identify risk factors for illness severity and mortality among patients with COVID-19.

RESULTS AND DISCUSSION

The illness brought on by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), a new virus that swiftly spread over the world, was given the designation "COVID-19" by the WHO on February 11, 2020. It has been discovered that age and the existence of underlying comorbidity have the biggest effects on the risks of contracting the virus[17]. The records were identifying through initial electronic search using PubMed and Google Scholar, 48 articles were included initially and upon assessing the full text articles for eligibility, screening of the title and abstract, 30 articles were selected and from that 17 articles were excluded because of the following reasons such as insufficient data, non-English full text, western population and at last 13 studies were included for the review study. In 5,297 confirmed COVID-19 patients, 1155 patients had Diabetes mellitus as a major comorbidity. These 1155 patients were involved in the study based on the inclusion and exclusion criteria from 13 studies and most of the patients were male 660 (57.1%) and female were 495 (42.9%). Male patients had Diabetes mellitus as a major comorbidity in COVID-19 when compared to females [18].

PREVALENCE OF COMORBIDITIES IN COVID-19:

Study no.	Total patients (n)	Smokers (%)	HTN (%)	DM (%)	CVD (%)	CKD (%)	CLD (%)
1.	1561	1	8	9.8	3	0.7	0.5
2.	241	NR	14.9	7.8%	3.7*	NR	4.6
3.	453	NR	33.1	70.8	9.7*	1.7	2.6
4.	845	NR	41.6	50.1	13.3*	NR	NR
5.	52	4.0	NR	17.0	23.0	NR	NR
6.	191	6.0	30	19.0	8.0*	1.0	NR
7.	201	NR	19.4	10.9	4.0	1.0	3.5
8.	274	7.0	34.0	17.0	8.0	1.0	NR
9.	1099	12.6	15.0	7.4	3.8	0.7	NR
10.	61	6.6	19.7	8.2	1.6	NR	NR
11.	138	NR	31.2	10.1	19.6	2.9	2.9
12.	140	NR	30	12.1	8.6	1.4	NR
13.	41	7.3	14.6	19.5	15.0	NR	2.4

(*reported coronary heart disease only, NR – Not reported)

Table-1: The table shows the prevalence of co-morbidities in COVID-19 among 5,297 subjects, the percentage of co-morbidities varies from (1 to 12.6%) for Smokers, (8 to 41.6%) for HTN, (7.4 to 70.8%) for DM, (1.6 to 23.0%) for CVD, (0.7 to 2.9%) for CKD, (0.5 to 4.6%) for CLD. The frequency of comorbidities in severe MERS-CoV infections served as

the main outcome measure. The etiology of MERS-CoV can be connected to metabolic syndrome-related disorders such diabetes, hypertension, CAD/CVD, obesity, and associated underlying factors. It is well recognized that these conditions downregulate important host innate immune response mediators to disease. For instance, insulinopenia, hyperglycemia, and diabetes reduce the production of proinflammatory cytokines, such as interleukins (ILs) and interferon gamma (IFN-g), as well as the acute phase reactants that result from these cytokines, which compromises the host's innate and humoral immune systems[19]. All individuals with COVID-19 experience fever, dry cough, sore throat, exhaustion and Diarrhoea as their main symptoms. There is no precise data regarding the various symptoms experienced by Diabetic patients, and they are more common among other individuals. However, there is consensus that diabetes people have more advanced symptoms[20,21].

BASED ON SEVERITY

Study no.	Total patients (n)	DM (n%)	ICU admission in non-Diabetes patients (%*)	ICU admission in Diabetes patients (%*)
1.	1561	9.8	7.8	17.6
2.	241	7.8	15.8	36.8
3.	453	70.8	1.5	7.1
4.	845	50.1	14.0	18.9

Table-2: The Prevalence of COVID-19 among Diabetes in ICU population. Only 4 studies compare the ICU admission in Diabetes and non-Diabetes in that data suggests that patients of COVID-19 with Diabetes had more risk of ICU admission (36.8%) than patients of COVID-19 without Diabetes (15.8%). One research concludes by demonstrating the significant effects that severe COVID-19-related ICU stays have on patients and their families. While the severity of the acute disease was much greater than the long-term pulmonary implications, there was still a significant worldwide impact on the lives of patients and their families, with the majority reporting long-term consequences that interfered with their daily activities[22].

BASED ON MORTALITY

Study No.	Total patients (n)	DM (n%)	Survivors of COVID-19 with Diabetes (%*)	Non-survivors of COVID-19 with Diabetes (%*)
1.	1561	(9.8)	7.8	2.0
3.	453	(70.8)	62.6	8.2
4.	845	(50.1)	45.1	5.0
5.	52	(17.3)	3.9	13.4
6.	191	(18.8)	9.9	8.9
8.	274	(17.1)	8.4	8.7

Table-3: Prevalence of Survivors versus non survivors in COVID-19 with Diabetes

The above table illustrates the prevalence of Survivors versus non survivors in COVID-19 patients with Diabetes. The mortality / non-survivors rate ranges from 2 to 13.4% and the survivor's rate ranges from 3.9 to 62.2%. So, it clearly shows that the patients of COVID-19 with Diabetes also have less mortality rate.

According to the results, Diabetes should be regarded as a risk factor for the intensity of COVID-19 symptoms, and limiting exposure to corona sources is the best course of action. In a study made by Yang X *et al*., the patients were segregated as survivors and non survivors. With regards to treatment, they were treated with High flow nasal cannula (63.5%), Mechanical ventilation (71%), Prone position ventilation (11.5%), Extracorporeal membrane oxygenation (11.5%), Renal replacement therapy (17%), Vasoconstrictive agents (35%), Antiviral agents (44%), Antibacterial agents (94%), Glucocorticoids (58%) and Immunoglobulins (54%)[23, 24].

In a study conducted by Zhou F Y *et al*., it was concluded that the patients were being treated with Antibiotics (95%), Antivirals (21%), Corticosteroids (30%), IV Immunoglobulins (24%), High flow nasal cannula oxygen therapy (21%), Non-invasive mechanical ventilation (14%), Invasive mechanical ventilation (17%), ECMO (2%), Renal replacement therapy (5%) [25, 26]. Guan WJ. Ni ZY *et al.*, it was reported that the majority of the patients (58.0%) received IV Antibiotic therapy, (35.8%) received Oseltamivir therapy; Oxygen therapy was administered in 41.3% and Mechanical ventilation in 6.1%; Systemic glucocorticoids (18.6%); Anti-fungal medication in 2.8%; use of extracorporeal membrane oxygenation in 0.5%; use of CRRT in 0.8%; use of IV Immunoglobulin in 13.1%[27]. In the study most patients received Antiviral Therapy-Oseltamivir (89.9%), many received Antibacterial therapy (Moxifloxacin-64.4%, Ceftriaxone-24.6%, Azithromycin-18.1%), Glucocorticoid therapy (44.9%), 1.45% of patients received CKRT, 76.81% of patients received Oxygen inhalation therapy, 10.9% of patients received NIV, 12.32 of patients received IMV and 2.9% of patients received EMCO[28].

It distinctly pretence that Diabetes mellitus was a major comorbidity associated with COVID-19 infection[29]. Programs that minimize exposure and illness risk in people who have diabetes must be implemented by health systems [30]. To obtain additional information, further investigation must be done in health care systems to reduce the exposure of risk of COVID-19 infection in diabetic patients [31]. In middle-class and low-income nations like India, the incidence of chronic illnesses is increasing due to aging populations and shifting food and lifestyle patterns. In order to enhance the defense against MERS-CoV and other respiratory illnesses in individuals with long-term conditions, a focused public health immunization campaign must be implemented.

STUDY LIMITATIONS:

The study adopted an extensive searching approach in this analysis by focusing on essential review tasks that encompassed all the studies that evaluated COVID-19 and diabetes. Nevertheless, since the study did not examine the grey literature, it is still feasible that we overlooked any unpublished data even though we did not have publication bias. Since there hasn't been enough study done thus far, we included some case studies and case series among the included studies. Furthermore, a bias in the group under examination existed, which makes sense given that the Asian population was the source of the disease outbreak.

CONCLUSION

Initial studies found that the male patients had Diabetes mellitus as major comorbidity in COVID-19 when compared to females. The studies of prevalence of comorbidities in COVID-19 shows high prevalence of Diabetes makes it as a major comorbidity followed by Hypertension, Cardiovascular Diseases, Chronic Liver Disease and Chronic Kidney Disease. And by comparing the ICU admission patients of COVID-19 with Diabetes and without Diabetes, studies show that COVID-19 associated Diabetes patients have more risk of ICU admission. Then comparing the prevalence of survivors versus non-survivors shows that the COVID-19 patients with Diabetes also have less mortality rate.

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