Prevalence, Clinical Characteristics, and Clinical Outcomes of New-onset Diabetes Mellitus among COVID-19 Patients in Developing and Developed Countries: A Systematic Review

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ABSTRACT

Diabetes mellitus (DM) is linked to poor clinical outcomes and high mortality in Coronavirus patients. The primary objective of this systematic review was to determine the prevalence, clinical features, glycemic parameters, and outcomes of newly diagnosed diabetes in individuals with COVID-19 in developing and developed countries. By searching PubMed, Medline, Scopus, Embase, Google Scholar, and PakMediNet databases, an online literature search was conducted from March 2020 to November 2021. Guidelines for reporting systematic reviews and meta-analyses (PRISMA) were used. There were 660 publications found, of which 27 were original studies involving 3241 COVID-19 patients were selected. In the COVID-19 patients with new-onset diabetes, mean age was 43.21±21.00 years. Fever, cough, polyuria, and polydipsia were the most frequently reported symptoms, followed by shortness of breath, arthralgia, and myalgia. The developed world reported (109/1119) new diabetes cases (9.74%), while the developing world reported (415/2122) (19.5%). COVID-19 new-onset diabetic mortality rate was 470/3241 (14.5%).

Key Words: *COVID-19, New onset diabetes mellitus, SARS-CoV-2, Prevalence, Clinical outcomes, Developing countries, Developed countries.*

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INTRODUCTION

SARS coronavirus 2 (*SARS-CoV-2*) is a new enveloped RNA beta-coronavirus that causes severe acute respiratory syndrome. In early 2020, the WHO declared COVID-19 a global pandemic.[1,2] The virus can be disseminated by asymptomatic patients or by infected individuals. COVID-19 individuals can have no symptoms, mild disease, or serious illness with multi--organ failure and death. COVID-19 mortality ranges from 0.7 to 10.8%.[3,4] Survival decreases, and more problems emerge in advanced age groups and patients with underlying comorbidities. This has been a source of concern for people living with chronic conditions such as Type 1 diabetes mellitus (T1DM).[5]

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Diabetes mellitus (DM) is a common chronic metabolic illness that causes significant morbidity and mortality globally. Diabetics are more prone to major consequences like SARS and multi-organ failure.[6] Diabetic individuals have a more severe COVID-19 manifestation. The condition of diabetic ketoacidosis is prevalent. A few patients with normal HbA1c and no family history of diabetes presented with new-onset hyperglycemia. COVID-19 patients have developed new-onset diabetes globally.[7] COVID-19-related DM raises management concerns. Eventually, they all get subcutaneous or intravenous insulin to maintain normoglycaemia while hospitalised. However, COVID-19 linked DM may acquire normoglycaemia with insulin faster than preexisting DM.[8] A register of COVID-19-related DM is required from various COVID centres and hospitals globally. Additionally, it is critical to determine if these patients will develop diabetes or enter remission.[9]

Several biological processes have been related to *SARS-CoV-2* infection in DM. To begin, DM decreases immunity. Chemotaxis, phagocytosis, and complement fixation are all affected by hyperglycemia. Second, DM can induce an inflammatory state characterised by higher levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor (TNF),

which has been related to multi-organ failure in *SARS-CoV-2* patients.[7,8] Third, in diabetic patients, the angiotensin-converting enzyme 2 (ACE2) receptor, which permits *SARS-CoV-2* to enter human cells, is upregulated, increasing the likelihood of virus infection. Fourth, COVID-19 virus can infect endocrine pancreas cells expressing ACE2 receptors, limiting insulin production and aggravating or causing DM.[8,9] DM may potentially be caused by insulin resistance caused by high interleukin-6 and tumour necrosis factor-alpha levels in COVID-19 patients. Hyperglycemia increases the susceptibility of lung cells to viral infection and replication.[9,10]

COVID-19 and DM are dependent on one another. Diabetes is associated with a poor prognosis for COVID-19. These patients had to develop new-onset DM and severe DM complications such as diabetic ketoacidosis (DKA) and hyperosmolarity.[7,8] Diabetes prevalence has risen sharply in developing countries in recent decades. Despite this, many published works focused on the impact of pre-existing DM on COVID-19 clinical course and outcome.[8,10] There are few data on the prevalence, clinical characteristics, types, and outcomes of new-onset DM in COVID-19 patients. To provide reliable data on newly diagnosed diabetes in COVID-19 patients, large-scale studies are now required. Therefore, the objective of this study was to assess the prevalence, clinical characteristics, types of newly diagnosed DM, glycemic parameters, and outcome of newly diagnosed DM in COVID-19 patients from developed and developing countries.

METHODOLOGY

This study used PRISMA (Principles for Reporting Systematic Reviews and Meta-Analyses) guidelines.[11] Because this was a systematic review, no IRB approval was required. Eligibility criterion for this systematic review was determined using the PICOS criteria.

PubMed / Medline / Scopus, Embase, Google Scholar, and PakMediNet were searched for all peer-reviewed articles published from March 2020 to November, 2021. Synonyms, Boolean operators, and truncation strategies were used to include as many articles as possible. 'New-onset diabetes', 'newly diagnosed diabetes', 'transient hyperglycaemia', and 'secondary hyperglycaemia' are all search terms that can be used in conjunction with 'COVID-19'. The search was restricted to the English language. Additionally, the reference lists of relevant articles were sorted through in order to identify additional studies that met the criteria.

This review included only observational studies that provided data on the number or percentage of newly diagnosed diabetes among COVID-19 patients. COVID-19 (lab-confirmed or clinically diagnosed) and new-onset DM were considered regardless of age, gender, or nationality. Non-peer-reviewed papers, COVID-19 patients with pre-existing diabetes and hyperglycemia, letters to editors, editorials, commentaries, review articles; animal studies, and publications in languages other than English were excluded from this review.

Newly diagnosed diabetes was defined as new-onset diabetes when an individual has been diagnosed with diabetes for the first time, they have no prior history of the disease and have fasting plasma glucose (FPG) levels less than or equal to 7.0 millimol/L or random blood glucose levels less than or equal to 11.1 millimol/L (RBG) levels or less than or equal to 6.5 percent (HbA1c).

After retrieving titles and abstracts, two authors checked for inclusion criteria. The remaining full texts were then screened for insufficient data and duplicates. At this stage, studies and cases in case series were double-checked. Three reviewers used standard data extraction formats to extract data from included studies. The extracted data included the type of study, the first author, the year of publication, the country of publication, the number of patients, their age, gender, symptoms, and glycemic parameters findings in COVID-19 patients admitted to the hospital. The review also included data on the number of newly diagnosed diabetes cases, the type of newly diagnosed diabetes mellitus, the time of diagnosis, the definition of newly diagnosed diabetes, and clinical outcomes. Author's disagreements were resolved by consensus.

The Newcastle–Ottawa Scale was used to assess study quality (NOS). This scale assesses both cross-sectional and cohort studies. Selection, comparability, and exposure/outcome are each given a maximum of four, two, or three points. On this scale, high-quality studies get a 7, while moderate-quality studies get a 5–7. Using the Joanna Briggs Institute (JBI) tool, the authors assessed the risk of bias in case reports and case series. This tool asked nine questions about the target population, sample size, condition being measured, and statistical analysis. For the quality assessment, the questions in the checklists must be answered with yes, no, unclear, or not applicable. The risk of bias classification is high for 1–3 yes responses, moderate for 4–6 yes responses, and low for 7–8 or more yes responses.[12,13] The authors undertook a world population review data using the Human Development Index (HDI) to classify countries in developing and developed countries list. HDI ranges from 0 to 1. Countries with a score above 0.80 are considered developed, while those with a score below 0.80 are considered developing.[14,15]

All statistical analyses were performed using SPSS 24.0 (SPSS Inc. Chicago, IL, USA, 2020). The results are presented descriptively. Quantitative variables are summarised using mean and standard deviation, while qualitative variables are presented as frequencies (n) and percentages (%). Each case report/series contained individual-level data. The authors present all available data and the percentage of variables with missing data. Valid denominators were used to calculate percentages (*i.e.* denominator signifies the number of patients who have data for the characteristic of interest). Hozo *et al*. method was to used estimate the median, average, and standard deviation of variables found in many cohort studies.[16] Among the studies that included glycemic parameters measurements, the authors chose those that included laboratory measurements during hospital admission.

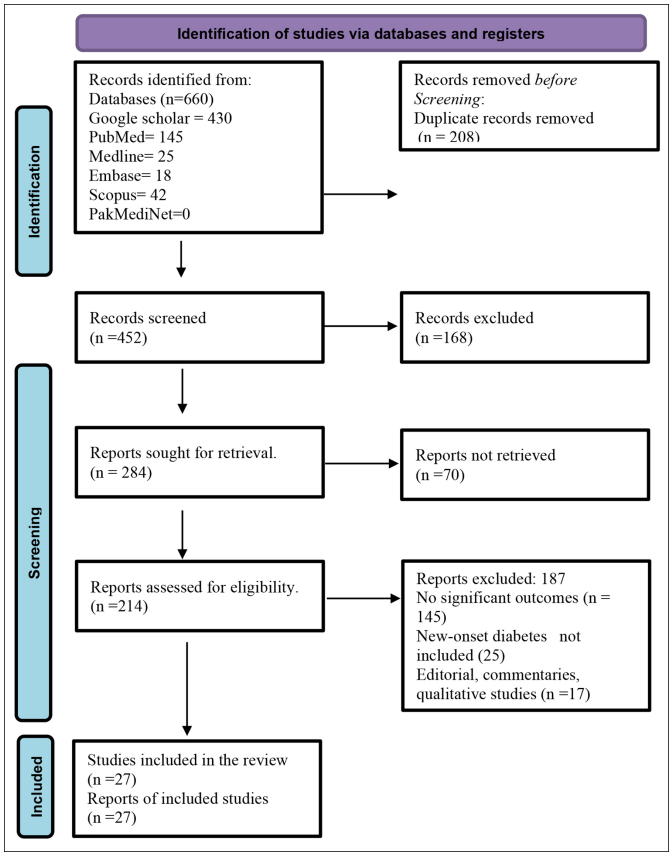

Figure 1: PRISMA flow chart of the study selection procedure.

RESULTS

A comprehensive literature review found 660 studies in databases such as Google Scholar, PubMed, Medline, Embase, Scopus, and PakMediNet (Figure 1). Two hundred and eight studies were removed due to duplication, and 168 were removed after the title and abstract were screened. The eligibility of 214 reports was determined, and 27 were selected for the final systematic review (Figure 1).[17-43]

To examine the onset of diabetes in COVID-19 patients, 27 observational studies were identified, including ten case reports, eight case series, eight cohort studies, and one cross--sectional study. The participants comprised 3241 COVID-19 patients with a non-significant prior history of diabetes mellitus. The clinical characteristics and symptoms of COVID-19 patients are summarized in the table below (Table I). Patients included in the study ranged in age from infants to adults and the elderly. The mean age of included COVID-19 patients was 43.21 ± 21.00 years, with a greater proportion of men 1636 (50.4%). Age was reported as the median (IQR) in six case series and seven cohort studies. In one cross-sectional study and one cohort study, the average age of all participants was mentioned (Table I). As a result of the distribution being approximately normally distributed in many studies, the median age was substituted for the mean and the interquartile range (IQR) for the standard deviation. Fever, cough, polyuria, and polydipsia were the most frequently reported symptoms, followed by shortness of breath, arthralgia, and myalgia. These were all hospital-based studies (Table I). Fourteen studies were conducted in developed countries, 13 in developing countries. The majority of studies were conducted in China (5 studies; 18.5%), India (5 studies; 18.5%) and Saudi Arabia (3 studies; 11.11%, Table I.

The mean random blood glucose level was 25.54 ±15.02. The mean ± SD of HbA1c was 91.85± 31.49 mmol/mol (Table II). Out of 3241 COVID-19 patients, (524/3241, 16.1%) had newly diagnosed diabetes from 27 studies. The developed countries reported (109/1119, 9.74%) new diabetes cases, while the developing world reported (415/2122, 19.5%). Eleven studies report Type 1 diabetes, while only three report Type 2 diabetes. The majority of studies 21(77.7%) detected newly diagnosed diabetes on the first day of hospitalisation. The mortality rate in new-onset diabetic patients with COVID-19 was (470/3241, 14.50%). The three studies did not report patient outcomes (Table III).

With respect to methodological quality of Newcastle–Ottawa Scale (NOS), cross-sectional study had moderate quality and low risk of bias and all cohort studies had moderate study quality and moderate risk of bias. The Joanna Briggs Institute (JBI) tool was used to assess the methodological quality of case reports and case series. Four studies had a moderate risk of bias, and fourteen studies had a low risk of bias, according to the results.

DISCUSSION

SARS-CoV-2 has been identified as the new virus causing this global pandemic. With severe insulin resistance and insulin insufficiency, COVID-19-associated diabetes is difficult to manage.[8,9] Although numerous studies have linked COVID-19 to DM, this is the first comprehensive review to synthesise clinical characteristics, prevalence of new-onset DM in COVID-19 patients, types, and outcomes in developed and developing countries. In this review, the most common COVID-19 patient's symptoms were fever, cough, polyuria, and polydipsia, as well as shortness of breath, arthralgia, and myalgia. This finding is in alignment with previous studies.[44,45] Diabetes mellitus is becoming more common all over the world, is a big public health problem, and is a big problem in the medical field. Diabetes mellitus long-term illness that is very serious can reduce a person's life expectancy, contribute to making their quality of life worse, and cost more to cure. The disease characteristics, prevalence, mortality rates and symptoms, differ broadly among different regions of the world.[5,7] This finding suggests that, in addition to fever, cough, and dyspnea, diabetes screening is critical in COVID-19 patients, and it seems that COVID-19 patients with these signs and symptoms need extra attention.

The overall mean age of the participants in this review was 43 years. The median age of hospitalized COVID-19 patients was 47 years in a previous study.[44] In developing countries, the majority of diabetics are between the ages of 45 and 65, whereas in developed countries, the majority over the age of 64. By 2030, diabetes will affect over 82 million people aged 64 and older in developing countries and over 48 million in developed countries, according to demographic trends.

Table I: Baseline characteristics of included COVID-19 patients.

Study type	First author (Ref)	Country	Sample size (n)	Age, Mean, median (IQR) (years)	Male N (%)	Female N (%)	Symptoms N (%)
Case report	Al-Naami 2020[17]	Saudi Arabia	1	46	1	0	Fever, cough, shortness of breath, irritability, increased thirst and urination for one week
Case report	Soliman 2020[18]	Qatar	1	0.7	N/R	N/R	Two days' history of fever, vomiting, 10% dehydration and rapid breathing
Case report	Rabizadeh 2020[19]	Iran	1	16	1	0	Seven-day history of fatigue, weakness weight loss, nausea, polyuria, polydipsia, and abdominal pain.
Case report	Daniel 2020[20]	India	1	15	0	1	Abdominal pain and vomiting
Case report	Marchand 2020[21]	France	1	29	0	1	Severe asthenia, fever, stiffness and dyspnea. Polyuria, polydipsia syndrome
Case report	Ali 2021[22]	Qatar	1	53	1	0	History of fever, cough, and shortness of breath for 2 days, associated with vomiting once.
Case report	Alfishawy 2021[23]	Egypt	1	17	1	0	Fever, palpitation, and cough of four-week duration
Case report	Albuali & AlGhamd2021[24]	Saudi Arabia	1	7	0	1	Polyuria, polydipsia, weight loss, fatigue and vomiting
Case report	Ordooei 2021[25]	Iran	1	10	1	0	History of polyuria, vomiting and polydipsia from ten days
Case report	Ghosh 2021[26]	India	1	60	1	0	Dull aching pain in his abdomen for the last 3 days associated with fever, cough, throat ache, malaise, increased thirst, excessive frequency of urination and generalised weakness
Case series	Kuchay 2020[27]	India	3	30,60,34	3	0	Fever or chills, Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache
Case series	Yang 2020[28]	China	*n* = 69 among 120 evaluated	61 years (IQR, 52 to 67)	34 (49.3)	35 (50.72)	Fever :62 (89.9), Cough: 45 (65.2), Sputum: 12 (17.4), Dyspnea: 30 (43.5), Fatigue: 26 (37.7), Diarrhea: 12 (17.4)
Case series	Alsadhan 2020[29]	Saudi Arabia	5	47 (42–62.5)	3 (0.6)	2 (0.4)	4 days' history of shortness of breath, cough, and confusion
Case series	Zavaleta 2020[30]	Peru	14	64 (42.5–71.2)	2(0.14)	12(85.71)	N/R
Case series	Reddy 2020[31]	India	2	45 (30–45)	2(2.0)	0(0.0)	General weakness, fever, loss of taste and mild dyspnea
Case series	Plasencia-Dueñas 2021[32]	Peru	13	64 (42.5–71.2)	3(0.23)	10(76.92)	N/R
Case series	Shankar 2021[33]	India	10	13 (11-15)	4(0.4)	6(0.6)	General weakness, fever
Case series	Suwanwongse & Shabarek 2021[34]	United States	3	18,51,64	2(66.66)	1(33.33)	Fever, cough, Anorexia, vomiting, nausea:1 (33.33) Fatigue:2(66.66),polydipsia:3(100), polyuria:3(100.0)
Cohort	Li 2020[35]	China	453	61.0 (49-68)	59(13.0)	394(86.9)	Fever: 77 (81.9), Cough: 61(64.9), Dyspnea: 35 (37.2), Nausea or vomiting: 9 (9.6), Fatigue: 47 (50.0), Diarrhoea: 12 (12.8), Poor appetite: 14 (14.9), Palpitation: 5 (5.3), Chest distress: 30 (31.9)
Cohort	Zhou 2020[36]	China	80	47 (35-56)	48 (60)	32(40)	Fever: 68 (85.00), Fatigue: 30 (37.5), Cough: 45 (56.25), Chest tightness: 27 (33.75) Dyspnea: 8 (10.00), Diarrhea: 9 (11.39)
Cohort	Wang 2020[37]	China	132	66 (56-(72)	68(51.51)	64(48.48)	Fever: 34 (77.3), Cough: 31 (75.6), Fatigue: 11 (26.8), Dyspnea: 32 (78.0), Myalgia: 6 (14.6), Diarrhea 3 (7.3)
Cohort	Zhang 2020[38]	China	166	62.7±14.2	85 (51.2)	81(48.79)	Fever: 16 (76.2), Cough: 15 (71.4), Dyspnea: 16 (76.4), Diarrhoea: 10 (47.6), Anorexia: 10 (47.6), Fatigue: 15 (71.4), Sore throat: 6 (28.6)
Cohort	Wang 2020[39]	China	605	59.0 (47.0, 68.0)	322 (53.2)	283 (46.8)	Fever: 463(87.4), Cough: 404 (72.8), Muscular soreness: 129 (25.6), Fatigue: 300 (56.8), Diarrhoea: 91 (17.8)
Cohort	Fadini 2020[40]	Italy	413	64.9±15.4	245(59.32)	168(40.6)	Fever: 272 (66.0%), Cough: 234 (63.9%), Dyspnea: 232 (61.9%), GI symptoms: 102 (28.5%)
Cohort	Lampasona 2020[41]	Italy	509	64.0 (56.2-71.5)	335(65.8)	174(34.1)	N/R
Cohort	Smith 2021[42]	USA	184	64.4 (21-100)	98(53.2)	86(46.7)	Hypoxia (83.7%) and fever 115 (62.5%)
Cross-sectional	Farag 2021[43]	Egypt	570	47.9 ± 10.9	317 (55.5)	253(44.3)	Fever: 70 (90.9%), Cough: 70 (90.9%), Dyspnea: 66 (85.7%), Diarrhoea: 11 (14.3%)
Total=27			3241	43.21 ± (21.00)	1636(50.4%)	1604(49.4%)	

Table II: Glycemic parameters findings of COVID-19 patients at admission.

Study type	First author (Ref)	Country	Random blood glucose (mmol/L)	HbA1c (mmol/mol)
Case report	Al-Naami 2020[17]	Saudi Arabia	36.5	87
Case report	Soliman 2020[18]	Qatar	31.7	64
Case report	Rabizadeh 2020[19]	Iran	28.41	108
Case report	Daniel 2020[20]	India	22.97	119
Case report	Marchand 2020[21]	France	20.5	105
Case report	Ali 2021[22]	Qatar	16.4	53
Case report	Alfishawy 2021[23]	Egypt	31.41	125
Case report	Albuali & AlGhamd2021[24]	Saudi Arabia	30.80	86
Case report	Ordooei 2021[25]	Iran	27.03	53
Case report	Ghosh 2021[26]	India	29.97	N/R
Case series	Kuchay 2020[27]	India	30.80, 32.30, 52.17	86,108, 108
Case series	Yang 2020[28]	China	6.5	N/R
Case series	Alsadhan 2020[29]	Saudi Arabia	23.3, 24	125,140
Case series	Zavaleta 2020[30]	Peru	43.35,38.79, 67.60	108,133,143
Case series	Reddy 2020[31]	India	N/R	75,112
Case series	Plasencia-Dueñas 2021[32]	Peru	N/R	N/R
Case series	Shankar 2021[33]	India	N/R	N/R
Case series	Suwanwongse & Shabarek 2021[34]	United States	27.53,44.12,19.59	90,112
Cohort	Li 2020[35]	China	4.97	N/R
Cohort	Zhou 2020[36]	China	N/R	N/R
Cohort	Wang 2020[37]	China	N/R	53
Cohort	Zhang 2020[38]	China	7.7	46
Cohort	Wang 2020[39]	China	9.769	N/R
Cohort	Fadini 2020[40]	Italy	7.3	50.3
Cohort	Lampasona 2020[41]	USA	9.93	57
Cohort	Smith 2021[42]	Italy	5.5	N/R
Cross-sectional	Farag 2021[43]	Egypt	11.56	42
Total=27			25.54 ± 15.02	91.85± 31.49

Increases are anticipated in the Middle East crescent, Sub-Saharan Africa, India, and Pakistan.[46] This is because chronic illnesses become more prevalent as people age. The current systematic review included more men (50.4%) than in previous studies (39.10% and 68.0%).[47,45] The sampling methodology, study subjects, study year(s), geographical location, variability within the studied subpopulation, and representation of sex and age groups in the population sample may have contributed to this heterogeneity.

The study also found that HbA1c and venous glucose levels of study participants were high on hospital admission, as in the previous study.[43,44] HbA1c values were reported for all newly diagnosed diabetic patients in COVID-19 patients in nineteen studies. On admission, a higher fasting blood glucose (FBG) level was a significant predictor of COVID-19 fatality. Diabetes was found to be associated with worsening disease severity and a worsening prognosis in patients with COVID-19.[44,48]

In 27 observational studies, patients infected with *SARS--CoV-2* had a 16.6% prevalence of newly diagnosed diabetes mellitus (1 to 29%). A proportion of 7.4% of COVID-19 hospitalised patients had DM according to Guan *et al*. From 8 studies involving 3700 patients, 14.4% of COVID-19 hospitalised patients had recently been diagnosed with diabetes.[49,50] Eleven studies report Type 1 diabetes, while only three report Type 2. This finding is in line with other research showing type 1 diabetes outweighs type 2.[51] It is currently unknown whether the COVID-19-associated new-onset diabetes is type 1, type 2, or a complicated type. Insulin deficiency caused by *SARS-CoV-2* infection may cause -cell death. Only a few case reports have been published on islet cell antibodies in newly diagnosed diabetes.[50,52] Perhaps some of the patients had a subclinical COVID-19 or ignored mild symptoms, triggering T1DM in genetically susceptible individuals. Another explanation is that some of these studies were done in areas where COVID-19 was common, while it was rare elsewhere.[50]

The developed world reported 109/1119 new cases of diabetes (9.74 %), while the developing world reported (415/2122) new cases of diabetes (19.5%). Diabetes is a significant public health problem as well as a clinical concern. The prevalence of diabetic type 1 diabetes is high in the world's poorest countries, but data on disease prevalence are scarce.[50,52] Noncommunicable diseases account for the majority of deaths in both developed and developing countries. Westernization and urbanization are held responsible for the increase. The current gradually shift from communicable diseases toward noncommunicable diseases upwards the burden in developing countries.[50,46] In developed countries, obesity, population ageing, and hypertension are all risk factors for diabetes. Variations in DM risk factors may also contribute to regional variation in prevalence.[46] This heterogeneity may have been exacerbated by population representation by gender and age group. Healthcare providers must educate diabetic patients on personal and environmental hygiene. The emphasis is on early diabetes detection, blood glucose control, patient education, diabetic programmes, and public awareness seminars.

Table III: Characteristics of included studies to assess new-onset diabetes mellitus and clinical outcomes among the COVID-19 patients.

Study type	First author (Ref)	Country	Number of newly diagnosed diabetes cases	Type of diabetes	Time of diagnosis	Definition of newly diagnosed diabetes	Clinical outcomes Discharge / Death
Case report	Al-Naami 2020[17]	Saudi Arabia	1	Type 1	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Death
Case report	Soliman 2020[18]	Qatar	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Discharge
Case report	Rabizadeh 2020[19]	Iran	1	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	Discharge
Case report	Daniel 2020[20]	India	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	Discharge
Case report	Marchand 2020[21]	France	1	Type 1	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	N/R
Case report	Ali 2021[22]	Qatar	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	Death
Case report	Alfishawy 2021[23]	Egypt	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Discharge
Case report	Albuali & AlGhamd2021[24]	Saudi Arabia	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Discharge
Case report	Ordooei 2021[25]	Iran	1	Type 1	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Discharge
Case report	Ghosh 2021[26]	India	1	Type 1 & DKA	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l	Discharge
Case series	Kuchay 2020[27]	India	3	Type 1	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Discharge
Case series	Yang 2020[28]	China	N/R	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l	Death: 16
Case series	Alsadhan 2020[29]	Saudi Arabia	2	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Death: 1
Case series	Zavaleta 2020[30]	Peru	4	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5	Death:2
Case series	Reddy 2020[31]	India	2	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	Discharge:2
Case series	Plasencia-Dueñas 2021[32]	Peru	4	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l	N/R
Case series	Shankar 2021[33]	India	3	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l	Discharge:5
Case series	Suwanwongse & Shabarek 2021[34]	United States	3	N/R	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6	Discharge:3
Cohort	Li 2020[35]	China	94	N/R	Third day of hospital admission	No prior diabetes history, FPG ³7.0 mmol/l	Discharge:74 Death:20
Cohort	Zhou 2020[36]	China	22	N/R	N/R	No prior diabetes history, RBG ≥11.1 mmol/l	N/R
Cohort	Wang 2020[37]	China	16	Type 2	First day of hospital admission	No prior diabetes history, RBG ≥11.1 mmol/l and HbA1c>6.5%	Death:16
Cohort	Zhang 2020[38]	China	21	N/R	Within 3 days after hospital admission	No prior diabetes history, FBG ≥7.0 mmol/l and HbA1c>6.5%	Discharge: 127 (76.5%) Death: 24 (14.5%)
Cohort	Wang 2020[39]	China	176	Type 2	First day of hospital admission	No prior diabetes history, FBG ≥7.0 mmol/	Death: 114(18.8%)
Cohort	Fadini 2020[40]	Italy	21	N/R	Exact time of diagnosis not reported	No prior diabetes history, HbA1c ³6.5% or RBG	Discharge: 298 (72.2%) Death: 48 (11.6%)
Cohort	Lampasona 2020[41]	USA	29	N/R	Exact time of diagnosis was not reported	No prior diabetes history, HbA1c ³6.5% or RBG	Death: 102
Cohort	Smith 2021[42]	Italy	49	NR	Exact time of diagnosis was not reported	No prior diabetes history	Death:63 Discharge:57
Cross-sectional	Farag 2021[43]	Egypt	65	Type 1 & 2	First day of hospital admission	No prior diabetes history, fasting plasma glucose [FPG] ≥126 mg/dL or random blood glucose [RBG] ≥200 mg/dL and HbA1c <6.5%	Death:62
Total=27			524				

COVID-19 had a mortality rate of 470/3241 (14.50%). According to one study, patients with newly diagnosed diabetes died at a higher rate than patients with no newly diagnosed diabetes (18.2% vs. 9.7%).[43] Similarly, an American study discovered that diabetic COVID-19 patients died at a higher rate than non-diabetic COVID-19 patients (288.8% vs. 6.2%).[53] COVID-19 death was reported as a single or composite outcome in a few studies. According to Barron *et al*.[54] COVID-19 caused the death of 1.50 percent (364/23,698 patients) of T1DM patients. In comparison, O'Malley *et al*. reported a 4% (5/113) mortality rate.[55] Chronic hyperglycemia has been associated with impaired immune function and a poor prognosis. This is the first study to demonstrate that diabetes exacerbates disease severity and impairs prognosis in patients with COVID-19.[54] Diabetes patients have a higher mortality and morbidity rate when it comes to serious medical conditions such as myocardial infarction. Additionally, elevated FBG predicts hospitalization in critically ill patients who do not have diabetes. Additionally, diabetes has been linked to severe disease following respiratory infections. Patients with COVID-19 and T2D who had well-controlled glycaemia had better outcomes, according to a recent study.[54,55]

Diabetic ketoacidosis (DKA) was common in COVID-19 and T1DM patients (6/11 studies, 54%). Other studies found higher rates of DKA in COVID-19 and T1DM patients, with O'Malley *et al*. reporting 24% (27/113),[55] Unsworth *et al*. reporting 36% (12/33),[47] and Atlas *et al*. reporting 51.7 percent (30/58).[56] DKA has been seen in people with COVID-19, indicating *SARS-CoV-2* directly affects pancreatic cells. In a SARS-CoV-1 hospitalized patient, immunostaining for ACE2 protein was strong in pancreatic islets but weak in exocrine tissues.[50,52] This should worry anyone concerned. This means that diabetic patients would seek care after complications started to occur if no diabetic survey was conducted among COVID-19 patients. After that, diabetic complications would be irreversible. Diabetes mellitus severely limits patients' activities.[50] Many studies have linked sub-acute viral injury to T1DM, an autoimmune disease characterized by pancreatic beta cell loss. Acute islet injury has been reported rarely. Acute diabetes has been linked to pancreatic islet viruses.[50] Hyperglycemia has been linked to *SARS-CoV-2* mortality. Virus-ACE2 receptor coupling may impair ACE2 function, linked to DM in ACE2 mouse models.[48,49] The virus can use the ACE2 receptor to replicate inside pancreatic islets, damaging cells like insulin-producing beta cells. Insulin

deficiency leads to acute DM in *SARS-CoV-2* patients. Newly diagnosed diabetes has a worse COVID-19 prognosis than no diabetes or pre-existing diabetes.[50]

Unhealthy lifestyle choices like excessive calorie consumption and lack of physical activity have been linked to rising non--communicable disease prevalence in low-resource settings. Multidisciplinary diabetes management is not readily available in low-resource settings. Obtained normoglycaemia and normolipidaemia require careful dietary management.[51,52] To prevent full-blown diabetes and other cardiometabolic disorders, COVID-19 patients with newly diagnosed diabetes should be closely monitored. With chronic inflammation and impaired immune response, diabetics appear to be more susceptible to severe illness from COVID-19, with poorer outcomes. Acute anti-inflammatory therapy with immunomodulation may be effective in COVID-19 diabetic patients, but further research is required.[53] Patient education on personal and environmental hygiene is needed. Education, programmes for diabetic patients and public awareness talks are all emphasised. Delays in taking action to flatten the COVID-19 pandemic curve will have disastrous consequences.[49] Dementia, diabetes, hypertension, and cardiac diseases will necessitate special protection for the elderly in developing countries it's time to use tele-consultation and tele-medicine to better control their blood sugars.[50]

The study has some strengths and limitations. This is the first study to consider new onset DM in COVID-19 patients from developed and developing countries. Two researchers independently searched, screened, selected, extracted, and assessed most studies. Unlike many other COVID-19 systematic reviews and meta-analyses, we excluded overlapping cohorts. Secondly, the authors were able to show the effect of glycemic control on COVID-19 mortality in terms of elevated HbA1c. The authors conducted a thorough literature search and carefully selected and scored studies. Finally, the review assessed new onset in COVID-19 patients. As a result, most studies correctly defined DM and inquired about the assessment method.

A meta-analysis was not possible due to a lack of relevant data. Clinical heterogeneity in the studied groups (some studies included adult patients and others included pediatric populations). The burden of new diabetes in COVID-19 patients varies by region and country. All included studies were not designed to estimate new-onset diabetes in COVID-19 patients. The small number of studies that screened for diabetes during serology *SARS-CoV-2* testing and the study sample size make it difficult to confirm that *SARS-CoV-2* solely causes DM. The clinical characteristics of COVID-19 diabetic patients could not be fully summarised due to a lack of published data.

This study included only a few patients with type 2 diabetes (T1DM). Then, more research will be done with more comprehensive data. These limitations highlight the need for larger global studies with community-based treatment of mild cases. With limited research, we could only use observational studies, case reports and series. Their sample sizes were small and their power was weak.

CONCLUSION

The prevalence of new-onset diabetes mellitus in COVID-19 patients ranged from 1% to 29%. Symptoms that were frequently observed included elevated blood glucose levels, fever, polyuria and polydipsia, shortness of breath, arthralgia and myalgia, nausea and vomiting in patients with newly diagnosed diabetes. The mean HbA1c, and venous glucose levels were all elevated in participants. From 27 studies, 524 patients with newly diagnosed diabetes were identified among 3241 COVID-19 patients. The developed world reported (109/1119) new diabetes cases (9.74%), while the developing world reported (415/2122) (19.5%). COVID-19 had a mortality rate of 470/3241 (14.50%). These patients should receive prompt treatment and should be closely monitored for the development of type 2 diabetes and other cardiometabolic disorders.

ETHICAL APPROVAL:
Ethics approval for this study is not necessary under Pakistani law as no patient data were collected.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
ND, MD, KJ: The conception and design of the study.
MKY, MSA, KJ: Acquisition, analysis and interpretation of data.
FAR, MD, KJ: Drafting the article.
MD, MSA, KJ: Revising it critically for important intellectual content.
All the authors have approved the final version of the manuscript to be published.

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