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The Case Fatality Rate of Alpha Covid-19 Variant in Patients with Concurrent Diabetes or Chronic Kidney Disease: A Systematic Review and Meta-analysis

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Abstract

Background: People with diabetes or chronic kidney diseases (CKD) are vulnerable to Covid-19. Our aim in this study was to estimate the fatality rate among people with diabetes or CKD infected by Alpha Covid-19 variant.

Methods: The authors searched PubMed, Scopus, and Embase from 1/12/2019 to 13/5/2020 to find studies that reported the fatality rate of Alpha Covid-19 variant among patients with diabetes/renal disease. A Random effects model meta-analysis was used to calculate the pooled case fatality rate (CFR). Then, a subgroup analysis was performed according to the sample size to find possible sources of heterogeneity.

Results: In total, 22 papers were studied for diabetes and 10 papers for CKD. The pooled CFR was estimated at 23% (95% CI: 0.18, 0.28) among diabetes patients and 31% (95% CI: 0.16, 0.48) among renal patients. High heterogeneity was observed among the studies (Diabetes: I^2=94%, t^2=0.0173, P<0.01), (CKD: I^2=69%, t^2=0.0457, P<0.01). The subgroup analysis indicated that the sample size had a significant effect on fatality rate estimation. In the diabetes patients, the pooled CFR of Alpha Covid-19 variant was 40% (95% CI: 22%-58%; I^2=91%, t^2=0.0797, P<0.01) among the studies with the sample size of less than 52 hospitalized patients. In the studies with equal or more than 52 patients, the pooled CFR was 14% (95% CI: 11%-17%; I^2=88%, t^2=0.0048, P<0.01). In addition, in renal patients, the pooled CFR was 62% (95% CI: 0.06%-100%; I^2=85%, t^2=0.3745, P<0.01) in the studies with less than six hospitalized patients, and the pooled CFR was 23% (95% CI: 16%-31%; I^2=0%, t^2=0.00, P=0.58) among studies with more than 6 patients.

Conclusions: People with either diabetes or CKD and infected with Alpha Covid-19 variant had a higher fatality rate in the general population. More care and vaccination is recommended for these patients. It is recommended that we calculate pooled estimation of the case fatality rate of the other variant of COVID-19 such as Beta, Delta, and Omicron in patients with chronic disease.

Keywords: COVID-19, Diabetes mellitus, Kidney diseases, Meta-analysis, Mortality

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Introduction

Diabetes mellitus is one of the metabolic disorders characterized by increased blood glucose level. The global diabetes prevalence in adults aged 20–79 is estimated to be 8.8% (uncertainty interval: 7.2–11.3%). People with diabetes have a higher risk of morbidity and mortality compared with the general population [1, 2]. These patients have impaired phagocytosis regarding neutrophils, macrophages and monocytes, neutrophil chemotaxis, bactericidal activity, and innate cell-mediated immunity [3]. Diabetes and hyperglycemia are reported to exacerbate inflammation by increasing the release of tumor necrosis factor α (TNFα) and Interleukin-10. Moreover, diabetes may lead to lung dysfunctions, such as decreased forced expiratory volume and forced vital capacity

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[4-7]. Diabetes has been reported to increase the risk of complications in severe acute respiratory syndrome (SARS), H1N1 influenza virus infection, and Middle East respiratory syndrome (MERS) [8-11].

Kidney damage involves a wide range of specific and non-specific clinical abnormalities, which may lead to impaired kidney function [5]. CKD is defined by established histological damage or a suboptimal (<60 mL/min/1.73 m^2) glomerular filtration rate (GFR) persisting for at least 3 months [12]. In 2017, CKD caused 1.2 million deaths and was the 12th leading cause of death worldwide. In addition, 7.6% of all cardiovascular disease (CVD) deaths (1.4 million) could be due to impaired kidney function. Together, deaths attributed to CKD ,which accounted for 4.6% of all causes of mortality [13].

Major causes of death in patients with *end stage renal disease* (ESRD are cardiovascular disease and infections. They account for up to 70% of all deaths in this group. It seems that the high susceptibility to infections is partly due to uremia, old age, comorbidities, and impaired immunity [14].

Alpha Covid-19 variant is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It affects the respiratory tract whose severity varies from asymptomatic or mild to severe disease. Although the current estimate of mortality rate of Alpha variant is < 5%, up to 15–18% of patients may get the severe illness, some of whom requiring intensive care unit (ICU) admission and mechanical ventilation. Old age and several comorbidities such as diabetes, hypertension, cardiovascular disease, and cancer are associated with poor prognoses [15, 16]. Some meta-analyses have reported that the mortality rate varies from 9.8% to 31.4% [17-19]. Another systematic review has reported that the mortality in general population was 5% [20]; however, there are limited reports in this regard.

The presence of comorbidities and impaired immunity in patients with diabetes and CKD are associated with poor outcome and high mortality. This is while the mortality reports of Alpha variant in patients with diabetes or CKD are controversial [21-24]. The aim of this study is to estimate the mortality rate of Alpha Covid-19 variant in patients with diabetes or CKD.

Methods

Protocol

The authors conducted the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement used in a previous study [25].

Eligibility criteria

In the current study, the researchers used studies which included people infected with coronavirus 2 (SARS-CoV-2). They had also been diagnosed with diabetes or CKD. No specific attention was paid to age, sex, and ethnicity. Death was the only clinical outcome. The studies were included for their design or publication date. The fatality rate was calculated as the number of deaths from Covid-19 was divided by all infected patients with diabetes or CKD.

Information sources

The authors searched PubMed, Scopus and Embase databases to find relevant papers. Furthermore, the references of the selected articles were screened to find other relevant studies.

Search

For over six months (December 2019 to mid-May 2020), the researchers conducted a comprehensive systematic literature search to identify eligible articles. The search terms including MeSH terms and text words were as follows:

Covid-19, SARS-CoV-2, diabetes, diabetes mellitus, T2DM, kidney diseases, nephritis or proteinuria, and mortality, fatality or death. The

search strategies are detailed in supplementary Table1.

Study selection

All records were imported into Endnote software ™ (version X8.1, Clarivate Analytics, Philadelphia, PA, USA). The duplicate papers were excluded. There authors also excluded conference papers, editorials, letters to the editor, and commentary articles. Data extraction and evaluation of literature were conducted independently by two groups of investigators, each consisting of two individuals. The controversial papers were discussed by the groups, and disagreements were resolved.

Data items

Microsoft Excel program was used to tabulate the study population data for each paper. The data included: first author, study type, year, country, number of patients with diabetes or CKD infected with Alpha variant, treatment, age, gender, hospitalization days, comorbidities, death, mortality, sever cases, and the methodological index for non-randomized studies scores (MINORS).

For the studies conducted on patients with diabetes, the researchers extracted the blood glucose level and HbA_{1c}. For studies on patients with CKD, the authors extracted surgery dates and other major details, CKD stage, blood urea nitrogen (BUN), creatinine, and estimated GFR (eGFR). The mortality rate was calculated as the percentage of patients who died and had Alpha variant, diabetes, or CKD.

Risk of bias in individual studies

The risk of bias in studies was assessed using MINORS checklist [26]. This tool is a valid method for assessment of the quality of non-randomized studies, whether they were comparative or non-comparative. This method also involves eight items for non-comparative studies. The score of each item ranged between zero and two (low to high quality), with a total score of 16 points. Two authors independently reviewed the eligible paper and scored them. Any disagreement over the scoring was resolved by discussing the issue with the second and the third author.

Summary measures

To estimate the pooled mortality rate, the authors performed meta-analysis, using R version 3.2.3. software. The mortality rate was determined for patients with Alpha variant, in two separate groups of diabetes and CKD. The random-effects model was used to calculate the pooled estimates. The heterogeneity among the studies was examined using I^2 index. Values of 0%, 25%, 50%, and 75% represented no, low, moderate, and high heterogeneity, respectively [27]. If a statistical heterogeneity was observed among studies, a subgroup analysis was conducted to determine the source of heterogeneity. Publication bias was determined by the funnel plot and Egger's test [28]. The statistical significance was set at $P<0.05$.

Additional analyses

Since inadequate sample size is an important issue in cross-sectional studies, the researchers conducted subgroup analyses based on the sample size. It was hypothesized that studies with a higher sample size had a higher validity to estimate the fatality rate, compared with the ones with a small sample size. Therefore, for the subgroup analysis, the researchers used the median sample sizes of all included studies to categorize them into two groups. Accordingly, the pooled fatality rate was estimated for each sub-group (studies with ≥ the median sample sizes of all studies *vs*. studies with < the median sample sizes).

Results

Study selection

Based on the search strategy, the authors identified a total of 228 articles for diabetes and 146 records for CKD. After eliminating the duplicate records through the EndNote software, 186 and 108 records remained in the diabetes and CKD groups, respectively. Two investigators [FR (Fatemeh Rajati) and FGv

(Farnia Ghanbarveisi)] screened both records (including patients with diabetes and patients with CKD) through EndNote software, independently. After discussing some disagreements, the authors selected 22 studies [20-24, 29-44] with 5629 diabetes cases from the diabetes file, and 10 studies [3, 23, 24, 36, 42, 45-49] were included with 148 cases of CKD .

From the selected articles, we assigned 69 and 61 papers to screen the title and abstracts for diabetes and CKD, respectively. Upon this step, 50 and 52 papers were excluded (Fig 1) from the diabetes and CKD studies, respectively. In the diabetes group, the patients' age ranged as follows: in eight studies the patients aged 50-60 years old; in 12 studies they aged 60-70 years old; and in one study, they aged 70-80 years old. Among the CKD studies, patients in one study aged 40-50 years old; in five studies, they aged between 50-60 years old; and in four studies, they aged 60-70 years old.

Details of the paper selection process are shown in Fig 1.

Lastly, three articles were added to the diabetes group and one to the kidney group during the review of the references. At the completion of the selection process, in the meta-analysis, 22 and 10 articles were respectively assigned to diabetes and CKD, respectively.

Study characteristics

The characteristics and the data extracted from the selected articles in each group are shown in the Tables 1 and 2, for diabetes and CKD, respectively.

Regional distribution of studies according to WHO regions is provided in Table 3. The study designs included in the present study are shown in Table 4.

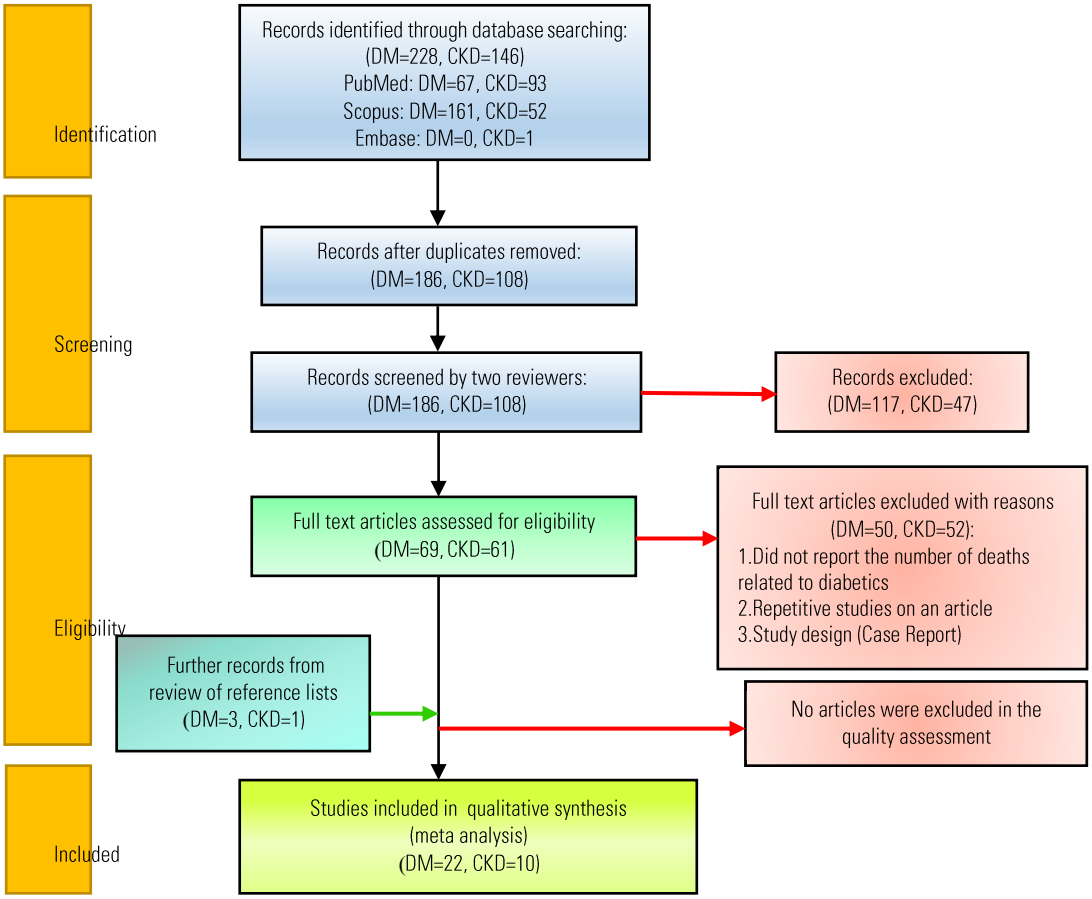

Figure 1. Flow chart of the study selection process: (DM) and (CKD)

Table 1. Characteristics of Included Studies (Diabetes)

n	First Author	Type of Study	Year	Country	All Patients	Number of People with Diabetes and Covid-19	Treatment	Age (median) (Years)	Sex male (%)	Hospitalization	Comorbidities (Patients with Diabetes): Hypertension (%)	Comorbidities (Patients with Diabetes): Heart disease (%)	Glucose (3.9–6.1) (mmol/L)	HbA_{1c} Normal range: (4-6) (%)	Number of death (COVID-Diabetes)	Case fatality rate(%)	Sever cases (%)	MINORS Score
1	Shi Q [34]	Retrospective study	2020	China	1561	153	-	64(range: 56.0-72.0)	49	yes	56.9	20.9	9.4(6.9 -13.3)	Non-survivors: 9.9% (8.4-11.4) vs. survivors: 7.9% (6.6-9.1)	31	20.26	20.3	13
2	(NCPERE) Team*[21]	Cross-sectional study	2020	China	44672	1102	-	54.5(Most: 30-79)	51.4	-	-	-	-	-	80	7.3	-	8
3	Guan WJ [20]	A nationwide analysis (retrospective case study)	2020	China	1590	130	-	13.4±61.2	58.9	yes	-	-	-	-	13	10.0	34.6	8
4	Kim N-Y[31]	Case reports	2020	South Korea	2	2	-	65.5	50	yes	100	-	-	Nonsurvivor: 11.4% vs. Survivor: 12.6%	1	50	100	13
5	Luo P[50]	Retrospective analysis	2020	China	283	104	Metformin group	63.0 (55.8–68.3)	51	yes	59.6	10.6	-	-	3	2.9	74	14
						179	No-Metformin group	65.0 (57.5–71.0)	57.5	yes	57	17.9	-	-	22	12.3	78.2	
6	Nikpouraghdam M[24]	A single center Study (A retrospective, epidemiological study)	2020	Iran	2964	113	-	56(46-65)	66	yes	-	-	-	-	11	9.73	-	8
7	Guo W [30]	Research article (A retrospective study)	2020	China	174	37	-	61(range: 55.0-69.0)	54.1	yes	27	32.4	-	-	4	10.8	-	15
						24 (Diabetic COVIDovid-19 patients without other comorbiditi	Insulin therapy pre-hospital patients)(7	61(range: 57.0-69.0)	50	yes	0	0	-		4	16.5	-	
															1	14.28		

						es)	Insulin dose increased in hospital patients)(7 Took oral medicine before admission and started insulin therapy after admission patients)(9								1 3	14.28 33.33		
8	Richardson S [33]	Observational study (case series)	2020	USA	5700	1808 1317	-	63(IQR: 52.0-75.0, Range: 0-107)	60.3	yes	-	-	-	-	224	12.38	57.6	8
9	Cariou B [29]	the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study (A nationwide multicentre observational study)	2020	Franc e	1317	Type of diabetes: Type 2: 1166 Type 1: 39 other: 71 Diagnosed on admission:4 1		69.8 ± 13.0	64.9	yes	1299 (98.63%)	qa1206 (91.57%)	-	(Normal range: 4-6)	140	10.6	410 (31.13%)	8
10	Wang F [35]	Original article (retrospective study)	2020	China	28	28		68.6 ± 9.0	75	yes	53.6	14.3	-	non-ICU (N = 14):7.5 ± 1.2 ICU (N = 14): 7.3 ± 0.90	12	42.85	50	13
11	Wang L [46]	Retrospective, single-center study	2020	China	339	54	-	71±8	49	yes	-	-	-	-	11	20.37	70.50	12
12	Wu C [41]	Original Investigation (A retrospective cohort study)	2020	China	201: (84 patients developed ARDS)	22: 16 of 84 6 of 117	- - -	51(interquartile range: 43.0-60.0) 51 51	63.7 63.7 63.7	yes yes yes	- - -	- - -	- - -	- - -	11 11 0	50 68.75 0	53 (26.4%) - -	13

13	Yan Y [42]	Original research (a single-center, retrospective, observational study)	2020	China	193	48	-	70 (IQR 62–77)	59.1	yes	50	27.1	11.31 (7.96 to 16.79)	Non-survivors: 7.4±1 vs. Survivors: 7.6±1.3	39	81.25	100	14
14	Zhang Y [51]	A retrospective cohort study	2020	China	258	63	-	65 (57–71)	60.3	yes	46	23.8	-	-	7	11.11	18 (28.6%)	14
15	Zhou F [23]	A retrospective cohort study	2020	China	191	36	-	56·0 (46·0–67·0)	62	yes	-	-	-	-	17	47.22	-	13
16	Chen T [36]	Retrospective study	2020	China	274	47	-	62.0 (44.0-70.0)	62	yes	-	-	-	-	24	51	-	9
17	Cao J [22]	Cohort study	2020	China	102	11	-	54(37-67)	52	yes 10(9.8%)	-	-	-	-	6	54.5	-	13
18	Wang Y [40]	To the editor (Cross-sectional study)	2020	China	344	64	-	64 (52–72)	52	yes	-	-	6.8 (5.7–9.0)	-	30	46.87	-	9
19	Du R-H [37]	A prospective cohort study	2020	China	179	33	-	57.6±13.7	54.2	yes	-	-	-	-	6	18.18	-	13
20	Shabto J.M [38]	A retrospective cohort study	2020	USA	49	49	-	59 (Range: 30–94)	27	Outpatient(isolation at home)	78	14	-	7.2 (range: 5.4–14.3)	2	4.08	-	11
21	Kong W [44]	Letter to the editor (Observational study)	2020	China	47	47	-	61 (range, 38–95)	48.94	yes	-	-	-	-	9	19.15	-	14
22	Chen Y [43]	Retrospective study	2020	China	904	136	-	56 (IQR 39.0–67.0)	46.57	yes	30.20	10.07	-	-	26	19.11	-	10

Abbreviations: (NCPERE) Team: * The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team; COVID-19: Coronavirus disease 2019; DM: Diabetes Mellitus; eGFR: estimated glomerular filtration rate; HbA_{1c}: Glycated hemoglobin. Data are presented n, median or %.

Table 2. Characteristics of Included Studies (CKD)

n	First Author	Type of Study	Year	Country	All Patients	Number of Covid19-CKD Patients	Age (median) (years)	Sex Male n(%)	Hospitalization	Comorbidities (all patients): Hypertension (%) N	Comorbidities (all patients): Diabetes N(%)	Surgery	Stages of CKD	BUN, mmol/L	Creatinine µmol/L	eGFR (ml/Min Per 1.73 m2)	Number of Death (COVID-CKD)	Case Fatality Rate (%)	Sever Cases (%)	MINORS Score
1	Banerjee D [48]	Editorial: special report	2020	England	7	7	54 (range 45-69)	57.14%	yes	6 (85.71)	3 (42.85)	kidney transplant recipients	3 of patients: 4-5 4 of patients: 3	- - - - - -	Patient 1: 350 180 450 Patient 2: 150 Patient 3: 132 Patient 5: 165 Patient 6: 187	(15–18) Patient 4: 23 Patient 7: (12-16) 45 48 31 47	0 1	0 14.28 25	42.85	12
2	Nikpouraghdam M [24]	A single center study(A retrospective, epidemiological study)	2020	Iran	2964	18	55(50-60)	%66.00	yes	59 (1.99)	113 (3.81)	-	-	-	-	-	3	16.66	-	8
3	Zhou F [23]	A retrospective, multicentre cohort study	2020	China	191	2	56·0 (46·0–67·0)	119 (62)	yes	58(30)	36(19)	-	-	-	Total (n = 191): Creatinine >133 µmol/L: n=8/186 (4%) Survivors (n =137): Creatinine >133 µmol/L: n= 3/132 (2%) Non-survivors (n =54): Creatinine >133 µmol/L: n= 5 (9%)	- - -	2	100	-	13
4	Valeri A.M. [49]	A retrospective study	2020	USA	59	59	63 (56–78)	33 (56)	yes	58(98.3)	41(69)	%8 Previous kidney transplant recipients	ESKD	-	-		18	30.50	8(14%)	14
5	Wang D [46]	Research (Retrospective case series)	2020	China	107	3	51.0 (36.0–	57 (53.3)	No (discharged	26(24.3)	11 (10.3)	-	-	4.2 (3.2–5.6)	Total (n = 107): 71 (60–86)	-	1	33.33	-	14

n	First Author	Type of Study	Year	Country	All Patients	Number of Covid19-CKD Patients	Age (median) (years)	Sex Male n(%)	Hospitalization	Comorbidities (all patients): Hypertension (%) N	Comorbidities (all patients): Diabetes N(%)	Surgery	Stages of CKD	BUN, mmol/L	Creatinine µmol/L	eGFR (ml/Min Per 1.73 m2)	Number of Death (COVID-CKD)	Case Fatality Rate (%)	Sever Cases (%)	MINORS Score
							65.0)		patients)					Survivors (n =88):						
														3.9 (3.0–4.7)	68 (58–83)	-				
														Non-survivors (n =19):						
														6.1 (4.9–10.5)	87 (71–130)					
6	Wang L [47]	Cross-sectional study	2020	China	116	5	54 (38–69)	67 (57.8)	yes	43 (37.1)	18 (15.5	-	-	Patients with Covid-CKD:						
														1 st week	32.08±8.58	937.61±114.62	14.43±7.34			
														2st week	30.66±9.64	955.47±141.09	15.96±8.72	0	0	39.65	12
														3st week	29.79±10.37	897.53±175.48	21.33±10.09			
														4st week	31.94±9.18	914.29±163.87	22.86±9.37			
7														Patients with Covid-Diabetes:						
	Yan Y [42]	Original research (Singlecenter,retrospective, observational study)	2020	China	193	4	64 (49 to 73)	114 (59.1)	yes	73 (37.82%)	48(24.87)	-	-	8.0 (5.1 to 11.0)	83.5 (65.8 to 102.3)	-	3	75	100	12
														Patients with Covid-Non-diabetes:						
														5.3 (3.6 to 9.0)	78.0 (58.0 to 100.0)	-				
8	Chen T [51]	Retrospective study	2020	China	274	5	68(62.0-77.0)	171 (62)	yes	93 (34)	47 (17)	-	-	-	-	-	4	80	-	9
9	Guan W [23]	Cross-sectional study	2020	China	1099	8	47 (35 - 58)	58.1%	Hospitalized patients and outpatients	165 (15.0)	81 (7.4)	-	-	-	-	-	2	25	37.50	8
10	Yiqiong M [52]	Cross-sectional study	2020	China	263	37	66 (55-81)	23 (62)	yes	-	-	-	-	-	-	-	6	16.21	-	8

Abbreviations: BUN: Blood Urea Nitrogen; CKD: Chronic Kidney Disease; Covid-19: Coronavirus Disease 2019; eGFR: Estimated Glomerular Filtration Rat. Data are presented n, median or %

Table 3. Regional distribution of studies according to WHO regions

WHO Regions / Topics	WPRO	PAHO	EMRO	EURO	AFRO	SEARO
Diabetes studies (%)	81.81	9.09	4.54	4.54	-	-
CKD studies (%)	70	10	10	10	-	-

Abbreviations: WHO: World Health Organization; WPRO: Western Pacific region; PAHO: Region of the Americas; EMRO: Eastern Mediterranean Region; EURO: European region; AFRO: African Region; SEARO: South-East Asia Region; CKD: Chronic Kidney Disease.

Table 4. Types of study designs

Type of Study / Topics	Retrospective	Observational	Cohort	Cross-sectional	Case report
Diabetes studies (%)	63.63	13.63	9.09	9.09	4.54
CKD studies (%)	60	-	-	30	10

Abbreviations: CKD: Chronic Kidney Disease

In the diabetes group, HbA_{1c} was reported in six studies, with a mean of 10.25 ± 3.32 in survivors and 10.65 ± 1.06 in non-survivors. In renal group, in two studies [48, 49] with 66 patients, stages of chronic kidney disease were reported. 62 patients were in the end-stage kidney disease (ESKD), and four patients were in stage 3 of CKD.

In studies done on patients with diabetes, the authors determined the prevalence of comorbidities among people with Covid-19. The prevalence of comorbidities was observed in nine studies. In eight studies [29, 32, 34, 35, 38, 42, 43], the prevalence of hypertension were higher among people with diabetes and Covid-19 than those in the second group [30]. In thirteen studies, these features could not be calculated. In CKD group, eight studies [23, 36, 42, 45-49] reported that some of their patients had comorbidities as hypertension. One study [24] reported that some of the patients had diabetes in addition to CKD. In one study [3], comorbidities were not taken into account.

Risk of bias among studies

Two of the authors reviewed and assessed the risk of bias in the studies separately based on the MINORS scale. (supplementary online files, Tables 2a-b). All the included papers had an acceptable quality in terms of their methodologies. For the diabetes group, the MINOR scores ranged from 8 to 14. This is while for CKD articles, the scores ranged from 8 to 13. All eligible papers scored above 8, and none of them showed a high risk of bias.

Meta-analysis

The results of meta-analyses showed that the fatality rate for Covid-19 in patients with diabetes was 23% (95% CI: 0.18, 0.28; $I^2 = 94\%, t^2 = 0.0173$, *P<0.01)* (Figure 2) .

The fatality rate for Covid-19 in patients with CKD was 31% (95% CI: 0.16, 0.48; $I^2 = 69\%, t^2 = 0.0457$, *P<0.01)*. A random effects model meta-analysis was used to calculate the rate (Fig 3).

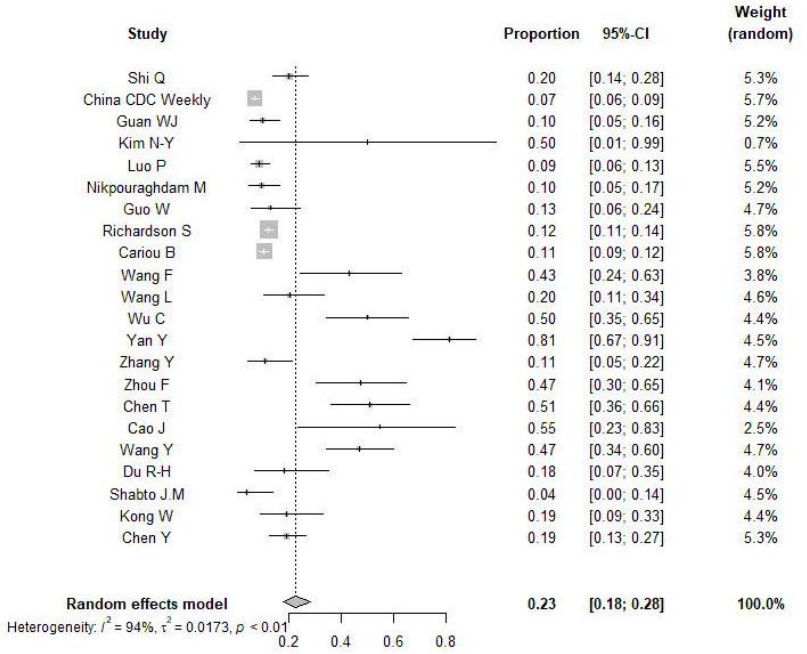

Figure 2. Meta-analysis of the case fatality rate of the COVID-19 in patients with diabetes

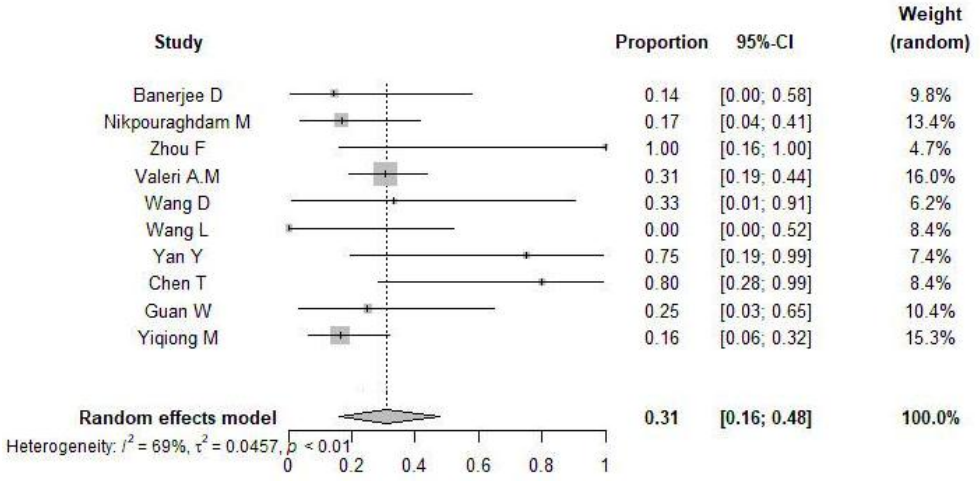

Figure 3. Meta-analysis of the case fatality rate of the Covid-19 in patients with renal disease

A funnel plot was drawn to test the publication bias in the diabetes (Supplementary 3) and CKD (Supplementary 4) groups. Since the heterogeneity was very high among the diabetes studies ($I^2 = 94\%$, $t^2 = 0.0173$, *P<0.01),* the researchers performed a subgroup analysis based on the median sample size (median= 52, higher and lower than 52 participants). From the 22 studies in the diabetes group, 10 studies consisted of less than 52 hospitalized patients with Covid-19 [22, 23, 30, 31, 35-37, 41, 42, 44]. The CFR of the COVID-19 in patients with diabetes (sample size <52) was 40% (95% CI:22%-58% ; $I^2 = 91\%$, $t^2 = 0.0797$, *P<0.01*)(Supplementary 5(a_1), Supplementary 5(a_2)). The pooled estimation of the CFR of studies with ≥52 diabetes patients was 14% (95% CI: 11%-17%;$I^2 = 88\%$,$t^2 = 0.0048$, *P<0.01*)supplementary 5(b_1) supplementary 5(b_2)). The researchers also calculated the median sample size for the CKD group, which was 6. This was considered the cutoff for the subgroup analysis. Therefore, due to the large heterogeneity among the CKD studies, ($I^2 = 69\%$, $t^2 = 0.0457$, *P<0.01)*, the authors performed a subgroup analysis between the two groups as follows: Four studies [3, 23, 24, 32] had less than six hospitalized CKD patients infected with Covid-19. Moreover, six papers [3, 23, 24, 45, 48, 49] comprised of more than six participants. The pooled CFR of the Covid-19 in patients with CKD (sample size <6) was 62% (95% CI:0.06%-100% ; $I^2 = 85\%$, $t^2 = 0.3745$, *P<0.01*) (Supplementary 6(a_1), Supplementary 6(a_2)). The pooled estimation of the CFR of studies with ≥6 CKD patients was 23% (95% CI: 16%-31%;$I^2 = 0\%$, $t^2 = 0.00$, *P=0.58*)(Supplementary 6(b_1), Supplementary 6(b_2).

Discussion

In this systematic review and meta-analysis, the authors estimated that the fatality rate among patients with diabetes or CKD, who were also infected with Covid-19, was about 23% and 31%, respectively. According to the literature published by WHO (World Health Organization), the overall fatality rate of Covid-19 among the general population has been estimated to be 5.67% [31]. In a previous study, the researchers found that the fatality rate was 21% among cancer patients [16]. It was noted that the fatality rate was higher among people with a chronic condition and infected with Covid-19, compared with those having a chronic condition [30]. This condition was even worse for patients who suffering from multiple morbidities, as reported by Kim's et al.'s study [31].

In another study by Froes's et al. (2020) the authors reported the prevalence of multimorbidity in 6.77% of the 36,244 patients infected with Covid-19. They demonstrated a 2.22 increased risk of hospitalization, ICU admission, and fatality for every additional morbidity (OR: 2.22 , CI 95%: 2.13-2.32) [53]. However, a similar fatality rate could not be found among patients with both Covid-19 and multiple morbidities. This is because the selected studies did not report the number of patients with multiple morbidities who had died.

The MINORS scores for included studies were between 8 and 14, confirming the high quality of the selected articles. Three out of six articles reported HbA_{1c}.. The HbA_{1c} level was higher in those who survived than in those who died (survivors: 12.6% versus non-survivors: 11.4%) [31], (survivors: 7.5±1.2% versus non-survivors: 7.3±0.9%) [35] ,(survivors: 7.6±1.3% versus non-survivors: 7.4±1%) [42]. However, differences in the fatality rates were not significant. Of note, the HbA_{1c} in one article was higher in patients who died (non-survivors: 9.9% (8.4-11.4) versus survivors: 7.9% (6.6-9.1) [34].

Since data were not sufficient for finding a rational relationship between HbA_{1c} levels and the severity or fatality rate of COVID-19, the

authors couldn't interpret or suggest a clinical decision on this matter.

In a study [34] that examined the risk of fatality in people with diabetes and Alpha Covid-19 variant, those who died were older, mostly male (71%), and had hypertension. Data suggested that the fatality rate was much lower among women than men. The lowest fatality rate was reported in a study by Lou's et al [32]. The effect of metformin therapy was examined on the fatality among people with diabetes and Alpha variant. Accordingly, the fatality rates were 2.9% and 12.3% among patients with or without metformin consumption, respectively. Interestingly, 51% and 57.5% of the patients with or without metformin consumption were men. The findings of this study suggested a significant reduction in the fatality rate among those who were taking metformin.

Chen et. al. in their study [43] evaluated the clinical characteristics and outcomes of people with diabetes and those who took glucose-lowering or blood pressure–lowering medications. The fatality rate was 9.30% (n=43, dead=4) in the metformin group, while it was 19.48% (n=77, dead=15) in those without metformin consumption. Comparing the fatality rate between the two groups, the authors found that using metformin played a significant role in the survival of patients with diabetes and Alpha variant. Other kinds of evidence in the reviewed literature supported this beneficial effect of metformin [32, 38]. This drug, as the first line of treatment among glucose-lowering agents, has a complex mechanism of action. It has anti-inflammatory effect that may reduce the fatality risk in people with severe Covid-19, in addition to its effects on lowering blood glucose [54]. Bramante's et al. (2020) observed a significant relationship between metformin use and reduced fatality in women with obesity or type II diabetes (Type 2 diabetes (T2DM)). It was among hospitalized individuals with Alpha variant. Gender-related findings are consistent with the fact that metformin reduces TNFα in women more than men. This also suggests that metformin protects against death from Covid-19, possibly through its effects on the release of TNFα [55]. Of these patients, 80% were taking metformin, and 31% were injecting insulin. Only in one of the selected studies, the fatality rate was as low as 4.08% [38]. In this study, the patients' HbA_{1c} level was not correlated with their symptoms and disease duration. This may be related to the small sample size. Most likely, the low fatality rate in these patients might be related to both the patients' gender and metformin use. As reported in Lou's study [32], the researchers observed a low fatality rate in female patients who were on metformin.

Based on the results of the study conducted by Chen et al. [43], people with diabetes and concurrent Alpha variant infection taking insulin, showed worse clinical outcomes than those who did not. These patients were at risk of poorer prognosis than those who did not take insulin (OR= 3.58, 95% CI 1.37,9.35; *P*= 0.009). The fatality rate in this group was 22.54% (n=71, dead=16) in the insulin group and 6.12% (n=49, dead=3) in those who did not take insulin. In this context, the researchers recommend that more clinical attention be paid to patients on insulin therapy.

Guo's et al. [30] followed up 24 patients with diabetes and Alpha variant, but without any other comorbidity. They found that the fatality rate was 10.89% among the patients, while the fatality rate was 14.28% among those who took insulin or an oral medicine before admission. Moreover, the fatality rate was 33.33% among those on oral medication before admission. Insulin therapy started at the hospital.

Based on the results of the current study and those reported by Chen et al. [43], there may be a relationship between insulin use and the clinical outcomes in patients infected with Alpha variant. However, this assumption is hard to prove due to insufficient evidence. This would be a worthy topic for investigation in a prospective cohort study. Yan et al [42]

evaluated the clinical characteristics and treatment outcomes of patients with both diabetes and a concurrent severe Covid-19 infection. They reported that most deaths occurred in men rather than women ($CFR_{Male} = {}^{30}/_{75} \times 100 = 90.90\%$,$CFR_{Female} = {}^{9}/_{15} \times 100 = 60\%$).

A similar result was reported by Shi et al. study [34]. Apicella et al. [56] argued that despite the similar gender distribution in people infected with Covid-19, (male 51%, female 49%), the fatality rate has been higher in men (2.8%) than in women (1.7%).

Cariou et al. [29] investigated the fatality rate of Alpha variant in both type I and type II diabetes in patients. They reported no fatality rate among type I diabetes patients younger than 65. Based on the results, the fatality rate of Alpha variant was higher among the patients with CKD than in those with diabetes. This could be due to multiple variables, such as fewer studies conducted on this subject, smaller sizes of samples, and lower prevalence of CKD than diabetes in the investigated patients.

It should be noted that heterogeneity was very high among the reviewed studies. The source of this heterogeneity can be justified by the sample size. In 21 out of 22 diabetes studies and 9 out of 10 CKD studies, patients were hospitalized. They were investigated in smaller sample sizes and in serious conditions. Understandably, these variables may easily raise the fatality rate. The other possible argument in support of the increase of fatality rate may be that patients suffered from a more severe form of Covid-19 due to their age and underlying comorbidities.

The subgroup analysis was based on the median number of patients with either Alpha variant and diabetes, or Alpha variant and CKD. It revealed that case fatality rate was 40% among the studies on less than 50 hospitalized patients who had both Covid-19 and diabetes. This is despite the fact that the rate was 14% in studies on a population of more than 50 inpatients or outpatients. In addition, the fatality rate was 62 % when less than 6 CKD patients with concurrent Covid-19 were studied at their hospitals; however, the rate was 23% in studies on more than six inpatients or outpatients. Thus, based on the results of the subgroup analysis, it becomes clear that the sample size has a significant effect on the reported fatality rate.

From the 22 reviewed studies on patients with diabetes in this report, 11 specifically evaluated patients with diabetes. In 10 studies, type two diabetes mellitus was investigated. In one study, types 1, 2 and other types of diabetes were monitored. Age was another variable that should be noted. In 9 out of 11 studies, the mean age of patients was over 60, and in two studies, the age was reported to be 55 or above. Diabetes had been diagnosed in all of the 11 articles as a risk factor for death or severe disease. Therefore, this risk factor should be considered the management of patients with Covid-19 infection. Finally, this study is the first meta-analysis that reports the fatality rate in patients infected with Covid-19 and concurrent diabetes or CKD. The authors believe in the appropriate study design and search strategy while using relevant databases for the purpose of this study. Although vaccination of the population makes the judgment difficult, the authors recommend conducting studies to calculate the pooled estimation of the case fatality rate of other variants of Covid-19 such as Beta and Delta.

Limitations

One of the limitations of the current study was that most of the patients were hospitalized. This may make the fatality rate unreal. Furthermore, because most of the studies available had been conducted in China, the authors couldn't assess the fatality of this unknown virus in other races and nations with varying economic status and more modern health facilities.

Conclusion

The pooled fatality rates of Covid-19 patients with diabetes/CKD were more than the ones for the general population. Since the details of fatality rate for patients with diabetes and CKD were not published, the authors could not conduct an in-depth analysis of the reviewed studies based on the patients' age, gender, and laboratory features such as HbA_{1c}, Serum Cr, BUN, and GFR. Therefore, researchers recommend that future studies review more papers with appropriate sample sizes and design for various nations. This should be done to better understand the fatality rate associated with SARS-CoV-2 and the effect of different drugs and treatment approaches in the treatment and prognosis of patients with Covid-19 along with other chronic conditions, such as cardiovascular disease, COPD, and hypertension.

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Authors' contributions

FR and MR did the literature search and designed the review strategy. Three authors (FG, ZMA and MD) independently screened the titles and abstracts toward the final selection of the eligible papers. MN and SS drew meta-analysis charts. FG drafted the first manuscript. FR and FG independently assessed the quality of studies in consultation with MN. ZMA wrote the introduction. FG and FR wrote the discussion, results and methods, and prepared the final draft of the manuscript. KT conducted the final revision and analysis. MK typewrote the final submission and coordinated the research team. All authors read and approved the final version of the submission.

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Conflict of interests

The authors declared no conflict of interest.

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