



COVID-19 in patients with diabetes: factors associated with worse outcomes

Negar Rezaei^{1,2} · Fateme Montazeri¹ · Mohammad-Reza Malekpour¹ · Ali Ghanbari^{1,3} · Sina Azadnajafabad¹ · Esmail Mohammadi¹ · Nazila Rezaei¹ · Shohreh Naderimagham^{1,2} · Erfan Ghasemi¹ · Mohsen Abbasi-Kangevari⁴ · Seyyed-Hadi Ghamari⁴ · Maryam Nasserinejad⁵ · Farzad Kaveh⁶ · Abbas Norouzinejad⁶ · Mohammad Mehdi Gouya⁶ · Alireza Raeisi⁷ · Farshad Farzadfar^{1,2} · Bagher Larijani²

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Abstract

Purpose Diabetes is one of the major comorbidities associated with COVID-19. We aimed to determine the clinical and epidemiological factors associated with the mortality of COVID-19 in diabetic patients in Iran, and also the impact of prescribed antiviral and antibiotics on patients' status.

Methods In this study, we used the national registry of hospitalized patients with Severe Acute Respiratory Syndrome (SARS) Symptoms with diabetes from February 18, 2020, to December 22, 2020. Demographic, clinical features, treatments, concurrent comorbidities, and their associations with mortality and severity outcomes were assessed using logistic regression.

Results 78,554 diabetic in-patients with SARS symptoms were included from 31 provinces of whom 37,338 were PCR positive for COVID-19. Older age and male gender are associated with COVID-19 mortality in diabetic patients. CVD is the most frequent comorbidity (42%). CVD, kidney disease, liver disease, and COPD are associated comorbidities which increased the risk of mortality. The mortality rate is higher in diabetic patients comparing to patients with no comorbidities, particularly in younger age groups. The frequency of antiviral, and antibiotics in COVID-19 positive patients was 34%, and 31%, respectively. Antibiotic treatment has no association with mortality in COVID-19 patients.

Conclusions Diabetic patients indicate higher mortality comparing to patients without any underlying comorbidities. Restrict strategies on increasing effective health care utilization must be considered in diabetic patients, especially in those with parallel underlying comorbidities. Regarding the antibiotic resistance issue and the noticeable use of antibiotics in diabetic patients, it is recommended to prioritize an antibiotic guideline prescription in COVID-19 patients for better stewardship by countries.

Keywords COVID-19 · Diabetes · Comorbidities · Antibiotics · Antiviral

✉ Farshad Farzadfar
farzadfar3@yahoo.com; f-farzadfar@tums.ac.ir

✉ Bagher Larijani
Emrc@tums.ac.ir

¹ Present Address: Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

² Present Address: Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

³ Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

⁴ Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁵ Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Science, Tehran, Iran

⁶ Center for Communicable Diseases Control, Ministry of Health and Medical Education, Tehran, Iran

⁷ School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Introduction

Diabetes is one of the major comorbidities associated with COVID-19 [1]. Despite the higher propensity of diabetic patients to other coronavirus infections in previous epidemics, the prevalence of diabetes among COVID-19 patients seems to be similar to the general population [2]. It is currently unknown whether diabetes predisposes people to COVID-19. However, it makes patients more vulnerable to severe forms of the disease resulting in a higher proportion of intensive care unit admission besides more mortality [3, 4]. The higher mortality rate and poor prognosis among diabetic patients with COVID-19 have been reported in different studies [5, 6]. Findings from a study conducted in the USA indicated a four-fold higher in-hospital mortality rate among diabetic and uncontrolled hyperglycemic patients. Additionally, in a Chinese study, the mortality rate in diabetic patients was 7.3% vs 2.3% for COVID-19 patients overall [7–9].

Age, sex, ethnicity, and low socioeconomic status, as well as concomitant medical conditions like renal impairment, may affect the prognosis of diabetic patients [2]. Several studies showed that poor glycemic control in diabetic patients increases the risk of complications [10, 11]. Furthermore, the impacts of glucose-lowering medication on the severity and fatality of COVID-19 have been reported [6, 12]. Although there are limited studies on antibiotics and antiviral treatment and the interactions with diabetes medications and a unique guideline on this issue, recent studies pointed to the specific effects of treatments for COVID-19 in diabetic patients, e.g. hydroxychloroquine reduces plasma glucose level leading to improve glycemic control besides the higher risk of hypoglycemia which needs special considerations in patients with diabetes [13, 14].

Thus, worse outcomes of COVID-19 in diabetic patients are more likely due to multiple factors that need to be more evaluated in different populations worldwide [2]. Regardless of the special attention to potential characteristics of antiviral and antibacterial drugs to treat COVID-19 [15], there is a lack of information about the impacts of these drugs on the outcomes of diabetic patients with COVID-19. We aimed to determine the clinical and epidemiological characteristics as well as the risk factors associated with the mortality of COVID-19 in diabetic patients in Iran and also the impact of prescribed antiviral and antibiotic on patients' mortality.

Methods

Overview

In this study, we used a national registry of hospitalized patients with Severe Acute Respiratory Syndrome (SARS) symptoms who are diagnosed with diabetes including patients with confirmed positive COVID-19 PCR from February 18, 2020, to December 22, 2020.

Case definitions

Diabetes is a self-report in this study. COVID-19 confirmed cases are defined as a positive result of laboratory tests for the COVID-19 from the respiratory specimens by the Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay. SARS cases were defined as diabetic patients with the following criteria: fever, respiratory symptoms, radiographic evidence of pneumonia, low or normal white-cell count with low lymphocyte count; with a history of travel to contaminated cities or direct contact with patients who have a fever or respiratory symptoms within 14 days before illness. All of these criteria were considered for hospitalization, but not necessarily all of them were required, and finally, the physician decided whether or not to hospitalize according to the patient's clinical condition. Severe cases are defined as diabetic patients who are admitted to ICU or needs a ventilator.

Collecting data

Demographics consist of gender (male/female) and age, comorbidities including cardiovascular diseases, chronic pulmonary diseases, kidney diseases, liver diseases, immune deficiency diseases, and malignancies (Yes/No). Signs and symptoms consist of fever, cough, dyspnea, myalgia, diarrhea, sore throat, and headache (Yes/No). Pregnancy status, Intensive Care Unit (ICU) admission status, ventilator assistance, COVID-19 PCR diagnostic test result, and clinical outcome, including death, under treatment, severe condition, and recovered were recorded using electronic forms from Hospital Information System (HIS). Moreover, there is a sub-sample of patients who have received prescribed drugs including antibiotics and antiviral treatment during a period of 4 months from initial point of pandemic. All electronic questionnaires were completed by skilled medical staff or physicians.

Statistical analysis

Data cleaning

The cleaning process was done, including managing duplicates cases, addressing missing data problems, recoding variables, and handling garbage records. Also, we had written text for prescribed drugs. So we used data mining via Python to recode them into variables, to calculate the association with outcomes.

Descriptive statistics

Frequency tables were used to describe data on comorbidities, signs, and symptoms, and treatment. Continuous variables (age and body temperature) have not normal distribution, so we reported a median \pm interquartile range of 5 to 95%. An appropriate map was used for showing the geographic distribution of COVID-19 mortality rates in patients with diagnosed diabetes.

Analytical statistics

First, to evaluate univariate analysis between mortality, severity, and recovery as outcome dependent variables and the demographic, comorbidities, signs and symptoms, pregnancy, antiviral, and antibiotics as independent variables, the models were built distinctly. The crude, as well as adjusted ORs, were calculated. The univariate analysis was used for calculating crude odds ratio (OR) and 95% confidence interval (CI) and eligibility to enter the final model. To conclude, the exposure factors with a p value of less than 0.2 were entered in the multiple logistic regression model. Consequently, a backward stepwise selection method was used to build multiple models that contained the independent variable groups of comorbidities, signs, and symptoms, that were independently associated with mortality. Adjusted ORs with p values of less than 0.05 and 95% CIs were reported for significant variables that were associated with outcomes. Confounding bias was identified as a consequence of the change in OR before and after adjustment for the confounding variable. Adjustment variables were different in each model based on the logic of the confounding role of the variables in the model. Age, sex, ICU, ventilator assistance, and treatment were variables that were used for adjustment in the multiple regression model. Consequently, the treatment was divided into four groups, antibiotics, antiviral, and pneumonia antibiotics protocol by NICE [16] and hydroxychloroquine. Finally, univariate and multiple logistic analysis was performed for the above-mentioned. The level of significance was considered as $p < 0.05$. The analyses have been done using R version 3.5.2.

Results

Between February 18, 2020, and December 22, 2020, 78,554 diabetic in-patients with SARS symptoms were registered in the ministry of health registry of Iran from 31 provinces of whom 37,338 were PCR positive for COVID-19 (47.5%). Median age (5–95 interquartile range) for hospitalized, and COVID-19 positive cases were 66(40–86), and 64(40–85), respectively. Females were slightly more than males in both hospitalized and COVID-19 PCR positive patients. Only 36% of pregnant hospitalized patients were PCR positive. The most prevalent comorbidities were CVD, kidney disease, and COPD. The most prevalent signs and symptoms were dyspnea, coughs, and myalgia. These were similar in PCR positive cases. Of patients who were ICU admitted, only 41% were PCR positive. This raised to nearly 48% in ventilator assistance. About 15% of registered patients were deceased, 56% of patients were recovered and 29% were under treatment and about 16% had a severe condition. The mortality rate is higher in diabetic patients comparing to patients with no comorbidities, particularly in younger age groups (13.9% vs 4.5% in under 20 year old, 7.8% vs 3.1% in 20–40 years old, 11% vs 7% in 40–60 years old, and 22.9% vs 20.7% in over 60 years old). This pattern is seen, as well, in ICU admission and ventilation requirement. More detail is determined in Table 1 and Fig. 1. The geographical pattern of mortality in diabetic in-patients with PCR positive COVID-19 was illustrated in Fig. 2.

In diabetic patients with COVID-19, the odds of mortality in patients aged more than 60, and under 20 are 3.4 and 1.9 times higher than the 20 to 40 age group, respectively, which demonstrated the higher risk of mortality in adults and children with diabetes. Males' odd of mortality is 1.34 times more than females. Mortality in COVID-19 patients are higher in COPD (OR = 1.45, 95%CI: 1.30–1.62), kidney disease (1.42, 1.28–1.57), liver disease (1.37, 1.11–1.70), and CVD (1.23, 1.17–1.30), respectively. Dyspnea (1.48(1.39–1.56)) was associated with higher mortality in diabetic patients, in contrast cough, fever, myalgia, and headache were associated with lower mortality. Although the odds ratio in non-diabetic patients were lower in many aspects comparing to diabetic patients, (such as CVD: 1.16, 1.12–1.20), but we could not compare the magnitude of the mortality effect size between two groups as the CI95% cross each other. The detail on OR crude (CI95%) is available in Table 2, Fig. 3.

During the first four months, nearly 34% of registered patients have used antibiotics and 24% used antiviral therapies. This was followed by 34% and 31% in PCR positive patients. The most prevalent prescribed antibiotic was from the cephalosporin drug category followed by macrolides and Broad-Spectrum hospital antibiotics like vancomycin.

Table 1 Descriptive data of diabetic and non-diabetic inpatients with COVID-19

	SARS Positive Diabetic Patients (N=78,554)	PCR Positive Diabetic Patients (N=37,338)
Age, N (%)		
(Mean ± SD)	64.6 ± 14.0	63.6 ± 13.6
<20 yrs. old	445 (0.6%)	129 (0.3%)
20 to 40 yrs. old	3245 (4.1%)	1,6137 (4.3%)
40 to 60 yrs. old	21,728 (27.6%)	11,618 (31.1%)
>60 yrs. old	53,136 (67.6%)	243,978 (64.2%)
Sex, N (%)		
Female	43,451 (55.3%)	20,368 (54.5%)
Pregnancy, N(%)	332 (0.4%)	119 (0.3%)
Comorbidity, N(%)		
CVD	33,746 (42.9%)	14,790 (39.6%)
COPD	4,733(6.03%)	1831(4.9%)
Kidney disease	5928 (7.5%)	2168 (5.8%)
Malignancy	1215 (1.5%)	401 (1.1%)
Liver disease	1153 (1.4%)	488 (1.3%)
Immune deficiency disorders	345 (0.4%)	150 (0.4%)
Sign & symptoms, N(%)		
Dyspnea	45,754 (58.2%)	22,344 (59.8%)
Cough	35,017 (44.5%)	18,973 (50.8%)
Body temp (Mean ± SD)	37.9 ± 0.8	38.0 ± 0.8
Fever	19,371 (24.6%)	10,271 (27.5%)
Myalgia	20,127 (25.6%)	10,923 (29.3%)
Sore throat	6529 (8.3%)	3469 (9.3%)
Headache	7937 (10.1%)	4262 (11.4%)
Diarrhea	3716 (4.7%)	1910 (5.1%)
ICU admission	8358 (10.6%)	3426 (9.2%)
Non-invasive ventilation	7867 (10.0%)	3771 (10.1%)
Outcome, N(%)		
Death	11,428 (14.5%)	6920 (18.5%)
Recovered	44,042 (56.1%)	20,214 (54.1%)
Under treatment	23,084 (29.3%)	10,204 (27.3%)
Sever Condition	12,820 (16.3%)	5593 (14.9%)

Remarkably, the Fluoroquinolones were used less than 4%, although they are the main drug for lung pneumonia infections. Kaletra followed by Oseltamivir are the two main antiviral prescribed drugs. The percent of prescribed Ceftriaxone, Ceftazidime, Cefepime, Ceftazidime, Cefixime, Cefazolin, Cefotaxime, CoAmoxiclav, Ampicillin were 17%, 0.3%, 0.3%, 0.2%, 0.2%, 0.1%, 0.06%, 0.05%, 0.01%, respectively from cephalosporin group in hospitalized patients with diabetes. This is 13.5% for Azithromycin and 0.08% for Clarithromycin/Erythromycin from macrolid group, 7.6% for Meropenem/Imipenem, 6.1% for Vancomycin, and 0.2% for Tazocin/Piperacillin/Tazobactam. The Recommended treatment for patients with pneumonia by NICE protocol includes

Tavanex/Levofloxacin or Tazocin/Piperacillin/Tazobactam or Ceftazidime or Vancomycin or Amoxicillin/CoAmoxiclav or Clarithromycin/Erythromycin was prescribed for less than 10% of patients. More information could be noticed in Table 3. Antibiotic treatment has no association with mortality.

Discussion

In diabetic patients with COVID-19, patients aged more than 60, and under 20 had 3.4 and 1.9 times higher odds of mortality compared to the 20 to 40 age group, which indicated the higher risk of mortality in elderly and young patients with diabetes. The odds of mortality in diabetic male patients was 34% more than female. COPD, kidney disease, liver disease, and CVD are associated comorbidities with higher mortality. The frequency of antiviral, and antibiotics were 34%, 31% respectively. Antibiotic treatment has no association with mortality in COVID patients.

Several studies pointed to age as a no modifiable risk factor for COVID-19 prognosis [5, 17]. The results of a retrospective study in Wuhan demonstrated that in diabetic people older than 70 years old, age is an independent risk factor for in-hospital death (HR 2.39, 95% CI 1.03–5.56) [3]. These data were consistent with similar studies showing that older age was associated with a higher mortality rate (Age ≥ 80 HR 4.79, 95% CI 3.62–6.32) of COVID-19 in diabetic patients [10]. Our study indicated that the diabetic in-patients with symptoms are more likely to be in the older age group parallel to similar other studies [2, 10]. Older age is likely to decline the immune responses leading to more susceptibility to complications of respiratory infection like acute respiratory distress syndrome and death [18]. Moreover, having diabetes for a longer period in older patients may lead to developing more complications of diabetes contributing to poor prognosis in COVID-19 [2].

The effect of being male on the mortality rate of COVID-19 is more significant in diabetic than non-diabetic patients [10, 19]. Data from NHS England introduced the male sex as a risk factor for the COVID-19 mortality rate (HR 2.39, 95% CI 1.53–1.65) [20]. These findings are parallel with our study results (OR = 1.34(1.26–1.41)). Lifestyle, type of occupation, habitual history (such as smoking and alcohol use), underlying disorders, and medications probably cause these remarkable differences between males and females. Thus, more special attention should be paid to this group to tackle this gender inequity in COVID-19 health care.

COPD with increased mucous production and obstacle of airways can lead to the development of hypoxemia. The inflammatory response, weak immunity, constant mucus production, use of respiratory corticosteroids, and structural damages of air paths are observed in COPD patients

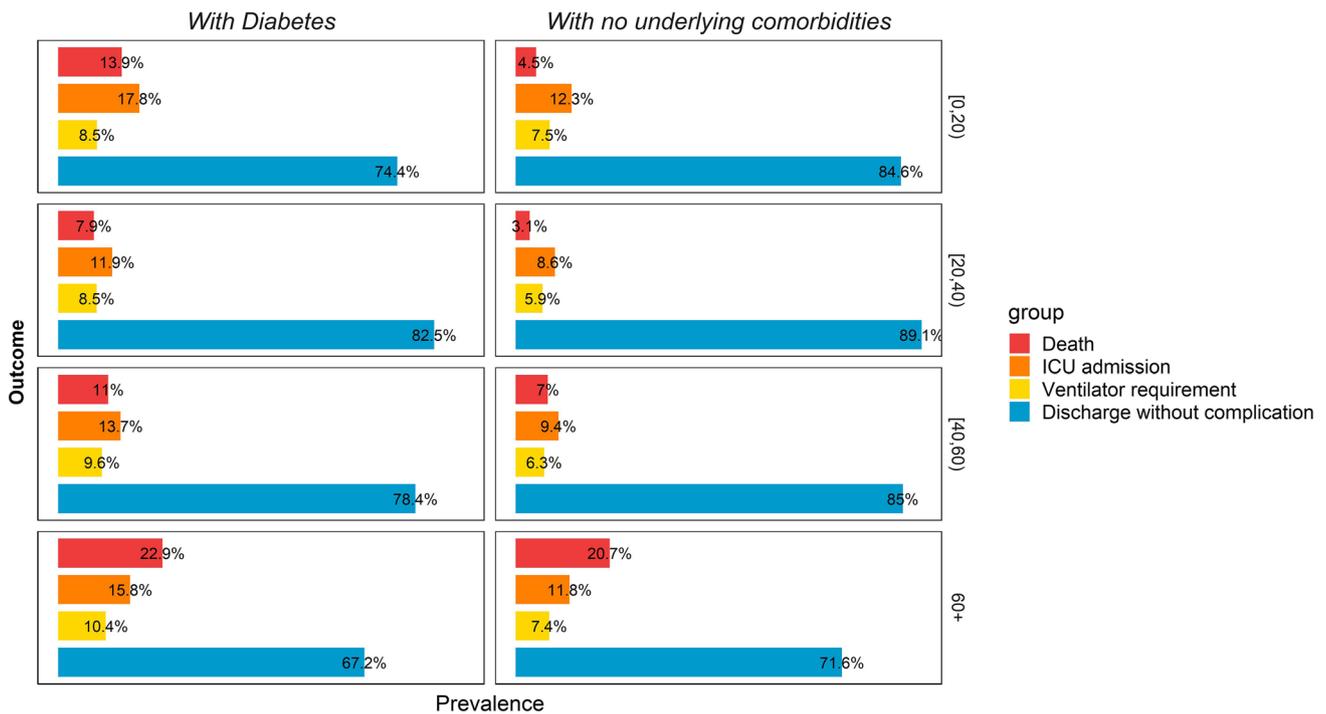


Fig. 1 Outcome of diabetic and non-diabetic inpatients with COVID-19

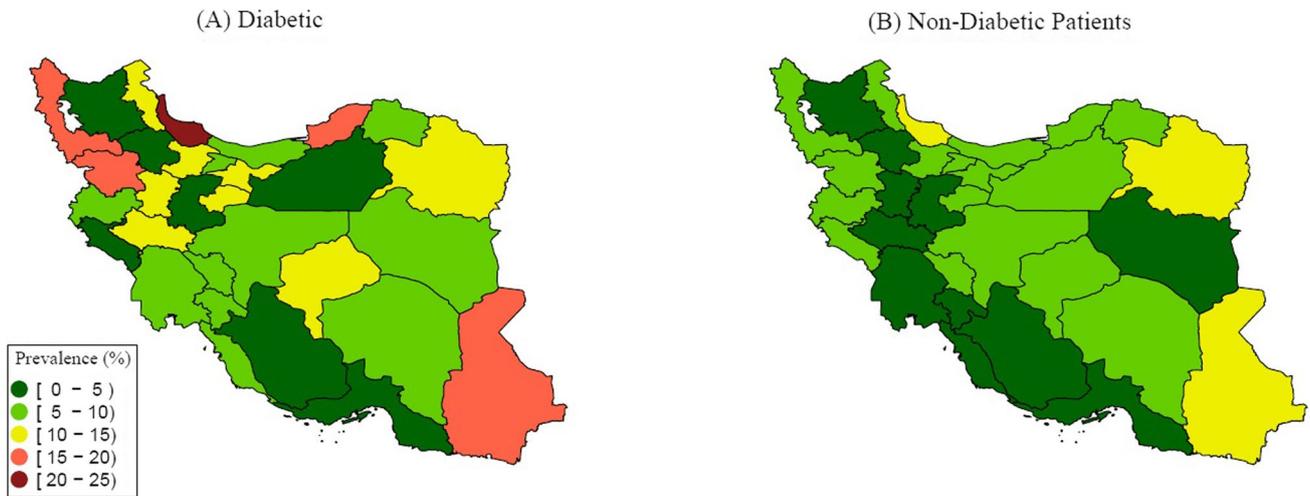


Fig. 2 Geographical pattern of age-standardized prevalence of death in diabetic and non-diabetic inpatients with PCR positive COVID-19

[21] which make the outcome of COVID worse when they are associated with diabetes. A study in China reported 50–52.3% of the total ICU admitted COVID-19 cases had COPD [21, 22]. The results of this study show a positive association between COPD and mortality in diabetic patients with COVID-19.

Individuals with cardiovascular comorbidities tend to develop a more severe form of COVID-19 resulting in a higher mortality rate [23]. Greater prevalence of

cardiovascular diseases among diabetic patients leads to a higher rate of death associated with diabetes. In this study, 43% of diabetic patients suffer from CVD. This comorbidity is significantly higher than the second common comorbidity, kidney disease, with 7.5% of diabetic patients. Underlying comorbidities contribute to worsening the outcome of diabetic patients infected by novel coronavirus COVID-19 and increasing the death rate. The role of some comorbidities like cardiovascular disease, hypertension, and chronic

Table 2 Odds ratio of mortality In diabetic and non-diabetic patients with positive COVID-19 PCR

Demographic	Diabetic with positive COVID-19 PCR (n=37,338)				Non-diabetic with positive COVID-19 PCR (n=233,611)			
	OR crude (CI 95%)	PV	OR adjusted (CI 95%)	PV	OR crude (CI 95%)	PV	OR adjusted (CI 95%)	PV
Age 20–40	Reference							
<20	1.90(1.12–3.23)	0.017	1.73(1.00–2.97)**	0.047	1.54(1.37-1.72)	<0.001	1.42(1.27–1.60)**	<0.001
40-60	1.45(1.20–1.75)	<0.001	1.36(1.12–1.65)**	0.001	2.35(2.23-2.49)	<0.001	2.26(2.14–2.39)**	<0.001
>60	3.49(2.90–4.19)	<0.001	3.11(2.58–3.74)**	<0.001	7.75(7.36-8.15)	<0.001	7.13(6.77–7.51)**	<0.001
Sex	1.33(1.26–1.40)	<0.001	1.34(1.26–1.41)**	<0.001	1.27(1.24-1.30)	<0.001	1.29(1.24–1.33)**	<0.001
Comorbidity								
Cardiovascular diseases	1.45(1.37–1.52)	<0.001	1.23(1.17–1.30)*	<0.001	1.92(1.86-1.98)	<0.001	1.16(1.12–1.20)*	<0.001
COPD	1.65(1.48–1.83)	<0.001	1.45(1.30–1.62)*	<0.001	2.05(1.94-2.17)	<0.001	1.48(1.40–1.57)*	<0.001
Malignancy	1.46(1.17–1.84)	0.001	1.23(0.97–1.56)*	0.085	2.95(2.71-3.21)	<0.001	2.51(2.29–2.75)*	<0.001
Kidney diseases	1.66(1.51–1.83)	<0.001	1.42(1.28–1.57)*	<0.001	1.96(1.82-2.11)	<0.001	1.47(1.36–1.59)*	<0.001
Liver disease	1.49(1.21–1.83)	<0.001	1.37(1.11–1.70)*	0.003	1.82 (1.58–2.10)	<0.001	1.61(1.38–1.87)*	<0.001
Immune deficiency disorders	1.01(0.67–1.52)	0.963	0.90(0.59–1.38)*	0.650	1.52(1.28-1.80)	<0.001	1.4(1.12–1.61)*	0.001
Sign & symptoms								
Fever	0.82(0.74–0.90)	<0.001	0.86(0.80–0.91)*	<0.001	0.78(0.74-0.81)	<0.001	0.88(0.86–0.91)*	<0.001
Cough	0.86(0.81–0.90)	<0.001	0.89(0.80–0.94)*	<0.001	0.86(0.84-0.88)	<0.001	0.87(0.85–0.89)*	<0.001
Dyspnea	1.56(1.48–1.65)	<0.001	1.48(1.39–1.56)*	<0.001	1.66(1.62-1.70)	<0.001	1.44(1.40–1.47)*	<0.001
Myalgia	0.73(0.69–0.77)	<0.001	0.79(0.73–0.83)*	<0.001	0.68(0.66-0.71)	<0.001	0.75(0.73–0.78)*	<0.001
Sore throat	0.83(0.76–0.92)	<0.001	0.92(0.83–1.01)*	0.108	0.76(0.73-0.80)	<0.001	0.91(0.87–0.95)*	<0.001
Diarrhea	0.85(0.75–0.97)	0.014	1.00(0.88–1.13)*	0.978	0.60(0.56-0.64)	<0.001	0.78(0.73–0.84)*	<0.001
Headache	0.62(0.57–0.69)	<0.001	0.74(0.67–0.832)*	<0.001	0.59(0.56-0.62)	<0.001	0.75(0.71–0.78)*	<0.001

*adjusted for age, sex, ICU admitting, Ventilator aid

**adjusted for ICU admitting, Ventilator aid, comorbidities

pulmonary disease is so important that the higher mortality rate among diabetic patients is attributed to these factors independently [3]. However, a study reported that the rate of death among diabetic patients remained higher than non-diabetic people after adjustment for cardiovascular comorbidities [8]. Patients with diabetic kidney diseases are more prone to infection complications due to chronic inflammation and subsequent immunosuppression. Also, renal impairment plays a role in developing cardiovascular diseases [24]. Moreover, the novel coronavirus COVID-19 can directly affect the kidneys by cellular injury or sepsis. This may lead to a cytokine storm, as well [25]. The prevalence of these comorbidities among diabetic patients is higher than the general population probably due to the nature of diabetes and consequent complications [19]. Thus, according to our results, more attention must be focused on diabetic patients with kidney disease.

A systematic review and meta-analysis on clinical symptoms of COVID19 reveal fever (88.7%, 95%CI 84.5–92.9%), cough (57.6%, 95%CI 40.8–74.4%), and dyspnea (45.6%, 95%CI 10.9–80.4%) were the most prevalent symptoms [26].

It seems dyspnea symptoms are more prevalent in diabetic in-patients in this study (45.6% vs 58.25) but this difference is not significant. Because it is located in a confidence interval of 95% of the prevalence of meta-analysis. However, other symptoms are less than recent reported studies (fever: 24.6% vs 88.7%, cough: 44.58% vs 57.6%). Only fever is significantly lower in diabetic patients of this study comparing to the result of the meta-analysis which could be a result of the immune response.

Of note, amid the COVID pandemic, health care utilization has been reduced especially for patients with chronic medical conditions leading to more morbidity and mortality [27] which is parallel with the mortality rate in this study (22%). Diabetes is a complex disease that should be managed continually by health care providers and patients closely [28] which needs health care infrastructures to facilitate patients management during COVID pandemics. According to our results, the high mortality rate of diabetic patients with COVID-19 might raise concerns for policy-makers in Iran to improve health care utilization for these patients.

Fig. 3 Odds ratio of mortality in diabetic patients with positive COVID-19

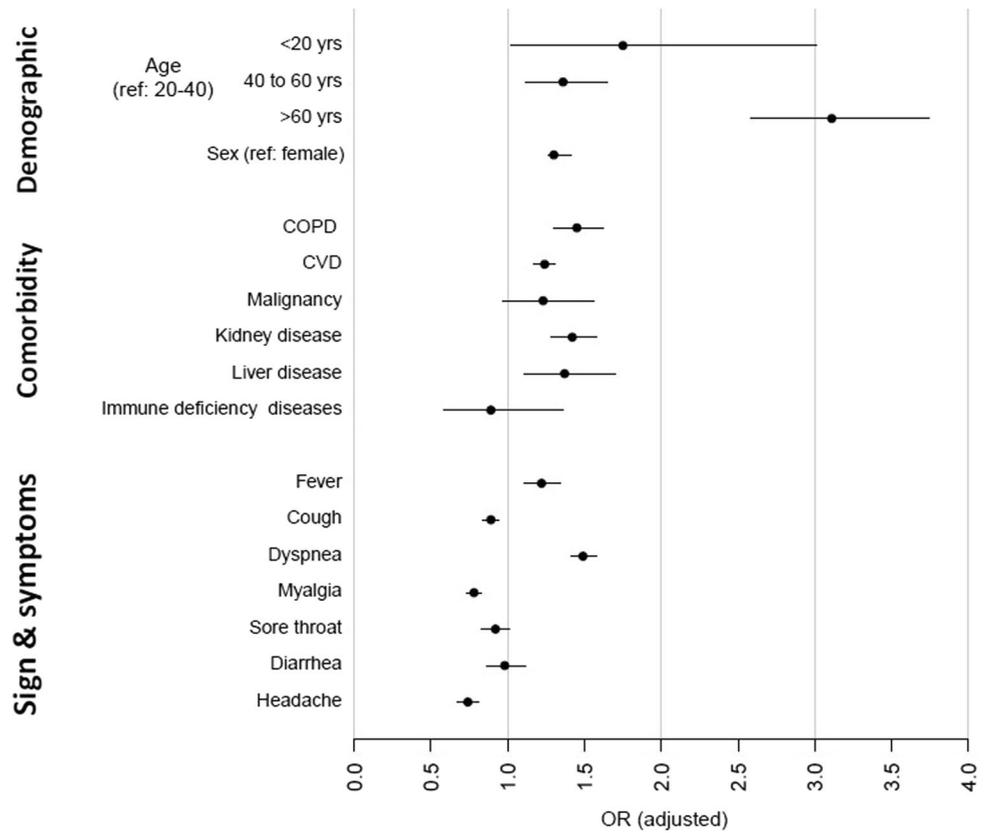


Table 3 Antibiotic and anti-viral treatment in diabetic patients with SARS symptoms, hospitalized, COVID positive PCR during 4 months

Diabetic Patients With SARS Symptoms	Hospitalized (N=21,247)	COVID PCR Positive (N=8235)
Antibiotic treatment	7267(34.20)	2845(34.55)
Anti-viral treatment	5133 (24.16)	2633(31.97)
Types of antibiotics		
Cephalosporin	3892(18.32)	1467(17.81)
Macrolide	2894(13.62)	1276(15.49)
Broad-Spectrum Antibiotic	2228(10.49)	854(10.37)
Fluoroquinolone	701(3.30)	341 (3.97)
Clindamycin	209(0.98)	53 (0.64)
Metronidazole	44(0.21)	2(0.02)
Aminoglycoside	27(0.13)	6(0.07)
Other Drug		
Hydroxychloroquine	5916(27.84)	2689(32.65)
Antiviral Treatment		
Kaletra	3312(15.59)	1674(20.33)
Oseltamivir	2593(12.20)	1455(17.67)
Ribavirin	235(1.11)	117(1.42)
Atazanavir	19(0.09)	12(0.15)
Interferon	5(0.02)	4(0.05)
Recommended treatment for patients with pneumonia ^a	1762 (8.29)	755(9.17)

^aTavanex/Levofloxacin or TazocinPiperacillin/Tazobactam or Ceftazidime or Vancomycin or Amoxicillin/CoAmoxiclav or Clarithromycin/ Erythromycin

During the COVID-19 pandemic, many efforts have been made to find appropriate and cost-effective available treatments [29, 30]. Despite the higher mortality risk in patients with specific comorbidities, there is still a paucity of information on the potential effects of recommended treatments on the prognosis of COVID-19 in diabetic patients [29, 31]. Due to the anti-inflammatory, anti-thrombotic, and anti-viral effects of chloroquine or hydroxychloroquine especially on SARS-CoV-2 in vitro, these drugs have been initially approved by the United States food and drug administration (FDA) in treating COVID-19 hospitalized patients [32]. However, subsequent analysis revealed that hydroxychloroquine has no beneficial effects on post-exposure prophylaxis and treatment in COVID-19 [33]. Moreover, several side effects have been reported for hydroxychloroquine e.g. cardiac toxicity including cardiomyopathy, heart failure, and rhythm disturbance, retinopathy, kidney injury, and liver problems [34]. Hydroxychloroquine may also cause hypoglycemia, particularly in patients on insulin or sulfonylureas [2]. Thus, this drug should be used with caution especially in diabetic patients. Despite the several side effects of this drug in diabetic patients as well as the lack of effectiveness in COVID-19 treatment, hydroxychloroquine is widely used in Iran. Our results show that about 30% of COVID-19 positive diabetic patients have been received hydroxychloroquine during their hospitalization. It seems that national COVID-19 treatment guidelines in Iran need to be frequently updated. Moreover, the results of this study reveal that antibiotics have no association with mortality in COVID patients. Also, we have a high-frequency use of high-cost antibiotics like imipenem and vancomycin. Studies reveal a wide range of antibiotic use in COVID patients worldwide [15, 35, 36]. Stewardship based on international guidelines and antibiogram performance [37] is needed to reduce antibiotic resistance in the age of COVID. Furthermore, this will support shrinking the economic burden of COVID-19 on individuals and governments. Although this is a cross-sectional registry and the absolute effect of any drug needs setting up clinical trials, but this result could help to develop a hypothesis on antibiotic resistance neglected issues during the COVID pandemic.

Of the strengths of this study is the large sample size of diabetic in-patient from all provinces of Iran which is the most attacked country by COVID-19. The data include most epidemiologic and clinical features with the utmost important outcomes which enable us to report a noble demonstration of the condition. Also, diabetes is a concern among non-communicable diseases in many countries. These make the result of this study valuable for future research and policymaking on these issues. Another advantage of this study is the duration of gathering data which covers a long period of the COVID epidemic in Iran. The main limitation of our study is that our registry data is limited to hospital cases and

may not identify the underlying cause of death, particularly in the absence of extensive COVID-19 testing. In addition, the registry data included comorbidities such as diabetes, based on self-report as a binary variable. Although, self-report is acceptable in the field of research, but clinically, it may be responsible for some sort of residual bias which could not be avoided. Moreover, lab data on glycemic control of diabetic patients were not provided in the registry. Future population-based longitudinal studies are needed for resolving these issue. Also, the data on diabetes drugs were not available in the registry and the data on antibiotic and antiviral treatment were in Persian text and only available during a subset of early 4 month period of pandemic, although Python text mining enables us to report these data.

Given the nature of diabetes which is multifactorial and syndemic, the inter-relationship between diabetes and COVID-19 should trigger more research to understand specific mechanisms of the virus that might contribute to worsening symptoms and outcomes in diabetic patients. The demographic and social factors may affect both diabetes and COVID, simultaneously. There is a huge chasm between developing and developed countries in this regard. So, increasing the capability of controlling this vicious cycle is needed to be focused in low and middle-income countries which are more prone to inequity in the quality of care and health utilization.

Regarding the antibiotic resistance issue and the diversity of antibiotic and antiviral treatment in the COVID pandemic worldwide, and the noticeable use of antibiotics in diabetic patients, it is recommended to prioritize an antibiotic guideline prescription in COVID-19 patients for better stewardship by countries. This is true in the case of antiviral therapy.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval and consent to participate The study was ethically approved by the Ethical Committee of National Institute for Medical Research Development, Tehran, Iran (ID: IR.NIMAD.REC.1399.185).

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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