



Research article

Clinical characteristics and risk factors for disease severity and mortality of COVID-19 patients with diabetes mellitus in Kazakhstan: A nationwide study



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ABSTRACT

Background: Diabetes mellitus (DM) is associated with higher risk of developing infectious disease and COVID-19 is not the exception. There is a need to generate more data on clinical characteristics and risks of COVID-19 patients presenting with DM. In this retrospective study we aimed to report on demographic features, clinical data, and outcomes of COVID-19 patients with DM in comparison with age- and sex-matched patients without DM.

Methods: This was a retrospective study that relied on the nationwide data on all COVID-19 patients who were diagnosed from 14 March to 18 April, 2020. Overall, there were 31 cases with DM for which we randomly matched 4 patients without DM by age and sex.

Results: COVID-19 patients with associated DM had less beneficial outcomes and more severe disease course both at hospital admission and final diagnosis, as compared with the age and sex-matched non-DM patients. Diabetics were more predisposed to impaired breathing (29.0 % versus 4.9 % in controls), nausea/vomiting (6.5 % versus 0 % in controls) and weakness/lethargy (45.2 % versus 26.0 % in controls). Finally, 48.4 % of diabetics showed the signs of pneumonia on CT scans versus 20.3 % of non-diabetics ($p = 0.001$), and 32.3 % of DM patients were admitted to intensive care units as compared with just 5.7 % of non-DM patients ($p < 0.001$).

Conclusion: There is a need to envisage early status monitoring and supportive care in this vulnerable category of patients to enable better prognosis.

1. Introduction

Nowadays the world is in the grips of the novel coronavirus (CoV) named SARS-CoV-2 and the infection it causes named COVID-19 [1]. As currently reported by the World Health Organization (WHO), more than 40 million cases were identified globally, with the death toll already exceeding 1 million [2]. The beginning of the epidemic can be traced back to November 2019 and it has originated from Wuhan, China [3]. This highly contagious CoV reached nearly every nation of the world and was deemed a pandemic by the mid of March 2020 [4].

At present there is neither approved vaccine nor specific treatment for COVID-19. The infection spreads between humans by means of a close contact from predominantly symptomatic individuals, but asymptomatic carriers can also transmit it although to a lesser extent [5]. The incubation period is estimated to be between 2 to 11 days [6]. Most individuals have mild symptoms, reported in about 87.4 % of Kazakhstani patients, which include cough, sore throat, fever, myalgia, and mild pneumonia at chest CT. The rate of moderate disease equaled 11.3 %, while 1.3 % showed signs of severe disease that was manifested by severe pneumonia, dyspnoea, respiratory rate >30 /min, and a very low blood saturation of

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oxygen ($\leq 93\%$). q [7]. Mild infections were observed to clear-up in a week, whereas severe cases commonly lasted for weeks and those patients experiencing acute respiratory and/or multiple organ failure may develop lethal outcome [6].

In China, lethal outcome was observed in 2.3 % of confirmed COVID-19 cases but it was more predominant in senile patients (8.0 % out of 70–79 year old patients and 14.8 % out of patients aged 80 years or more) or critically ill patients (49.0 %). Higher lethality was also seen in patients affected by cardiovascular disease (10.5 %), diabetes mellitus (7.3 %), chronic pulmonary disease (6.3 %), arterial hypertension (6.0 %) and malignant neoplasms (5.6 %) [8]. Still, fatality from COVID-19 was higher in Italy and constituted 7.2 % [9]. This fact was explained by a higher share of individuals aged 70 years or more [10]. Nevertheless, a number of countries including Russian Federation, Germany and South Korea reported on a lower lethality among COVID-19 patients [11]. These data should be treated with caution as there is inter-country variability in case definition and registration of fatality causes.

It is a well-known fact that diabetes mellitus (DM) is associated with higher risk of developing infectious disease and pneumonia is not the exception [12]. Besides, DM is a frequent finding in COVID-19 patients, accounting for as many as 10 % of all cases, according to some reports [13]. Moreover, underlying DM was found in 20–30% of nonsurviving COVID-19 patients [14, 15].

The incidence of diabetes mellitus in the Republic of Kazakhstan is growing every year. According to the data of the large epidemiological study NOMAD, which was conducted among both urban and rural Kazakhstani population (aged 20–79 years), 8.2 % of individuals were diagnosed with type 2 DM, and in 38.2 % of individuals pre-diabetes was identified. The prevalence of type 2 DM varied from 8.3 % (95 % Confidence Interval: 7.1–9.4 %) to 9.3 % (95 % Confidence Interval: 8.5–10.0 %) [16].

Thus, there is a need to generate more data on clinical characteristics and risks of COVID19 patients presenting with DM. In this retrospective study we aimed to report on demographic features, clinical data, and outcomes of hospitalized COVID-19 patients with DM in comparison with age- and sex-matched patients without DM.

2. Materials and methods

2.1. Data sources

This was a retrospective study that relied on the nationwide data on all COVID-19 patients who were hospitalized to the government-designated hospitals in Kazakhstan from 14 March to 18 April, 2020. Within this period, the Ministry of Health took approach to hospitalize all identified COVID-19 cases, regardless of their severity and relied solely on reverse-transcriptase PCR (RT-PCR) to confirm the diagnosis. Overall, there were 1961 hospitalized patients, of which we retrieved medical records on 31 cases with DM (1.58 %).

On the next step we applied the propensity score matching method for non-random matching of cases and controls that was aimed at creation of matched case-control pairs, which would be as similar to each other as possible. For each COVID-19 patient with DM we matched four COVID-19 patients without DM by age (± 2 years) and sex, following the strategy that was used in the earlier study [17]. In situations when more than 4 matches were available for each DM patient, we randomly selected out of those available.

2.2. Data extraction

Ministry of Health, Kazakhstan provided access to anonymized electronic medical records of COVID-19 patients solely to Semey Medical University, Kazakhstan. All medical records were reviewed by a team of experienced physicians – faculty members of Semey Medical University. Any incomplete medical records were omitted. The data extracted included patient's age, sex, disease history, history of DM and other

underlying comorbidities (arterial hypertension, chronic cardiac failure, ischemic heart disease, chronic kidney disease, and cerebrovascular disease), vital signs at admission and discharge (heart rate, breath rate, median systolic and diastolic blood pressure, SpO₂ and body temperature), laboratory parameters (blood glucose level, white blood cell count, C-reactive protein, blood biochemistry, etc.), description of chest computed tomographic (CT) scans and chest X-ray scans, severity of COVID-19 at admission and final diagnosis, treatment provided to patients in intensive care unit (ICU): supplemental oxygen, noninvasive mechanical ventilation, invasive mechanical ventilation; and presence or absence of lethal outcome. Besides, we retrieved the data on total length of hospital stay, coexisting risk behaviors (smoking and alcohol consumption) and COVID-19-associated symptoms (sore throat, chest pain, headache, diarrhea, nasal congestion, muscle pain, impaired breathing, vomiting/nausea, weakness/lethargy, smell and taste change, etc.).

2.3. Definitions used

COVID-19 was diagnosed in strict adherence to the WHO interim guidance [18]. Throat swabs with subsequent RT-PCR were used for confirmation of COVID-19 case. The diagnosis of DM was made in accordance with the guidelines of American Diabetes Association [19]. We identified pregnant women with gestational diabetes and patients with glucocorticoid-induced hyperglycemia and excluded them from the analyses. Our primary outcome was the presence of severe disease or in-hospital mortality in COVID-19 patients with DM, as well as associated risk factors. The secondary study outcomes were clinical characteristics, co-existing pathologies, laboratory findings, and treatment strategies in comparison between COVID-19 patients with and without DM.

2.4. Ethical statement

Before the study beginning, we obtained the permission from Ethical Committee of Semey Medical University, Semey, Republic of Kazakhstan. Because only anonymized medical records were available to the study team, the ethical committee waived informed consent.

2.5. Statistical analyses

Categorical variables were described as frequencies and proportions, while continuous variables were described as medians and interquartile ranges. We used the Pearson χ^2 -test and Mann–Whitney U-test, as appropriate. The level of significance of all statistical tests was preset at $P < 0.05$. The statistical tests were performed with the help of IBM SPSS Statistics 20 software.

3. Results

Although the average length of hospital stay was almost the same in diabetics and non-diabetics (15 and 14 days, respectively), there was a significant difference in disease severity at hospital admission and final diagnosis. Such, at the stage of hospital admission the proportion of diabetics at severe or critical condition constituted 22.6 % as compared with 3.2 % of non-diabetics. Accordingly, at the time of final diagnosis 41.9 % of diabetics were recognized as having severe or critical state in contrast with 4.0 % of non-diabetics. Moreover, DM as comorbidity to COVID-19 was significantly associated with in-hospital lethality (Table 1).

Table 2 presents the behavioral risk factors and presence or absence of DM. There were significantly more smokers and alcohol consumers among diabetics, which was rather surprising. However, it was not unexpected that a significantly higher proportion of diabetics had stroke or myocardial infarction in past history. Likewise, DM was more commonly associated with other comorbidities: chronic cardiac failure, arterial hypertension, ischemic heart disease, and kidney disease.

Table 1. General characteristics of population under study, (N = 155).

Variables		Diabetes Mellitus status				Test of difference	
		Controls (-)		Cases (+)		χ^2	p-value
		N	%	N	%		
Gender	Female	54	43.5	18	58.1	2.101	0.147
	Male	70	56.5	13	41.9		
Age (median; 25 th and 75 th percentile)*		34 (26; 47)		34 (26; 47)		-0.123	0.902
Age group	18–39	71	57.3	18	58.1	0.007	0.996
	40–59	45	36.3	11	35.5		
	60 >	8	6.5	2	6.5		
Ethnicity	Russian	8	6.5	1	3.2	1.849	0.397
	Kazakh	94	75.8	27	87.1		
	Other	22	17.7	3	9.7		
Number of bed days (median; 25 th and 75 th percentile)*		14 (6; 17)		15 (4; 17)		-0.378	0.706
Initial severity at hospital admission	Moderate	120	96.8	24	77.4	14.091	0.000
	Severe or critical	4	3.2	7	22.6		
Severity degree at final diagnosis	Moderate	119	96.0	18	58.1	34.712	0.000
	Severe or critical	5	4.0	13	41.9		
Outcome associated with COVID-19	Alive	124	100.0	29	93.5	8.105	0.004
	Died	0	0.0	2	6.5		

* Test of difference: Mann–Whitney U-test.

As for the symptoms at hospitalization stage, the median systolic blood pressure and breath rate were significantly higher in diabetics as compared with non-diabetics. Also, diabetics were more predisposed to impaired breathing (29.0 % versus 4.9 % in controls), nausea/vomiting (6.5 % versus 0 % in controls) and weakness/lethargy (45.2 % versus 26.0 % in controls). Such symptoms as taste and smell change, cough, hemoptysis, and dyspnea were more frequently reported for patients with DM. Finally, 48.4 % of diabetics showed the signs of pneumonia on CT scans versus 20.3 % of non-diabetics ($p = 0.001$) – Table 3.

Considering the laboratory data at hospitalization stage, there was significant difference in concentrations of monocytes, urea, C-reactive protein, and blood glucose between the study groups (Table 4). According to Table 5, admission to ICU was the only severity-associated factor, which reached the level of statistical significance when compared between the two study groups.

Based on analysis of outcomes and severity associated factors in groups of patients with different glucose levels, lung damage on CT-scan and admission to ICU were more prevalent in patients with serum glucose levels exceeding 7 mmol/L (Figure 1).

4. Discussion

Recent research has demonstrated that DM serves as a risk factor for severe COVID-19 illness [20]. This was also true for influenza A (H1N1) pandemic, which demonstrated the three-fold increase in hospitalization rate and admission to ICU among DM patients [21]. In Lombardy region of Italy, out of 1591 patients admitted to ICUs due to COVID-19, 17 % presented with DM [22]. In the USA, DM was identified in 6 % of non-hospitalized, in 24 % of hospitalized, and in 32 % of COVID-19 patients admitted to ICU [23]. Another study from the USA showed that the proportion of DM among patients hospitalized due to COVID-19

Table 2. Behavior risk factors and comorbidity, (N = 155).

Variables		Diabetes Mellitus status				Test of difference	
		Controls (-)		Cases (+)		χ^2	p-value
		n	%	n	%		
Smoking	No	111	90.2	22	71.0	7.812	0.005
	Yes	12	9.8	9	29.0		
Alcohol consumption	No	120	97.6	27	87.1	6.249	0.012
	Yes	3	2.4	4	12.9		
Past stroke	No	123	99.2	29	93.5	4.164	0.041
	Yes	1	0.8	2	6.5		
Past myocardial infarction	No	124	100.0	29	93.5	8.105	0.004
	Yes	0	0.0	2	6.5		
Chronic Cardiac Failure	No	123	99.2	29	93.5	4.164	0.041
	Yes	1	0.8	2	6.5		
Arterial hypertension	No	118	95.2	17	54.8	35.880	0.000
	Yes	6	4.8	14	45.2		
Ischemic Heart Disease	No	124	100.0	30	96.8	4.026	0.045
	Yes	0	0.0	1	3.2		
Kidney disease	No	120	96.8	19	61.3	33.732	0.000
	Yes	4	3.2	12	38.7		

Table 3. Symptoms at the stage of hospitalization, (N = 155).

Variables	Diabetes Mellitus status				Test of difference		
	Controls (-)		Cases (+)		χ^2	p-value	
	n	%	n	%			
Heart Rate (median; 25 th and 75 th percentile)*	78	72; 82	80	78; 85	-1.920	0.055	
SAP (median; 25 th and 75 th percentile)*	110	110; 120	120.0	110; 140	-2.666	0.008	
DAP (median; 25 th and 75 th percentile)*	80	70; 80	80	70; 90	-2.060	0.039	
Breath Rate (median; 25 th and 75 th percentile)*	18	17; 19	26	18; 28	-5.192	0.000	
SpO2 (median; 25 th and 75 th percentile)*	98	96; 98	96	94; 98	-1.461	0.144	
Body temperature (median; 25 th and 75 th percentile)*	36.6	36.10; 37.00	37.00	36.1; 37.6	-0.668	0.504	
Sore throat	No	94	76.4	24	77.4	0.014	0.907
	Yes	29	23.6	7	22.6		
Chest pain	No	108	87.8	25	80.6	1.078	0.299
	Yes	15	12.2	6	19.4		
Headache	No	93	75.6	26	83.9	0.962	0.327
	Yes	30	24.4	5	16.1		
Diarrhea	No	120	97.6	30	96.8	0.061	0.806
	Yes	3	2.4	1	3.2		
Nasal congestion	No	110	89.4	25	80.6	1.767	0.184
	Yes	13	10.6	6	19.4		
Muscle pain	No	116	94.3	28	90.3	0.648	0.421
	Yes	7	5.7	3	9.7		
Impaired breathing	No	117	95.1	22	71.0	16.431	0.000
	Yes	6	4.9	9	29.0		
Vomiting/nausea	No	123	100.0	29	93.5	8.040	0.005
	Yes	0	0.0	2	6.5		
Weakness/lethargy	No	91	74.0	17	54.8	4.332	0.037
	Yes	32	26.0	14	45.2		
Convulsions	No	119	96.7	30	96.8	0.000	0.994
	Yes	4	3.3	1	3.2		
Fatigue	No	109	88.6	29	93.5	0.647	0.421
	Yes	14	11.4	2	6.5		
Smell change	No	118	95.9	23	74.2	15.143	0.000
	Yes	5	4.1	8	25.8		
Taste change	No	117	95.1	25	80.6	7.222	0.007
	Yes	6	4.9	6	19.4		
Cough	No	107	87.0	16	51.6	19.276	0.000
	Yes	16	13.0	15	48.4		
Hemoptysis	No	114	95.8	24	77.4	11.287	0.001
	Yes	5	4.2	7	22.6		
Dyspnea	No	110	90.9	16	51.6	26.875	0.000
	Yes	11	9.1	15	48.4		
Lung damage on chest X-ray	No	100	81.3	22	71.0	1.606	0.205
	Yes	23	18.7	9	29.0		
Lung damage on CT-scan	No	98	79.7	16	51.6	10.140	0.001
	Yes	25	20.3	15	48.4		

* Test of difference: Mann–Whitney U-test.

constituted 31.8 %, which was substantially higher than that among non-hospitalized patients with mild disease course (5.4 %) [24]. A study conducted in Russian Federation on a large cohort of patients presenting with acute respiratory distress syndrome secondary to COVID-19 revealed the underlying DM in 25 % of cases [25].

However, the worse outcomes for COVID-19 on the background of DM could be explained by the presence of other comorbidities, which have the potential to deteriorate the disease course. The sample of such comorbidities could be made of cardiovascular disease and obesity that frequently accompany DM. According to the findings of retrospective case series composed of 3615 COVID-19 patients who presented to a large academic hospital system in New York City, 21 % had the body mass index (BMI) within the range of 30–34 kg/m², while 16 % of them

had BMI ≥ 35 kg/m². In patients aged <60 years, obesity and severe obesity were associated with 1.8-fold and 3.6-fold increased risk for admission to ICU, respectively. Meanwhile, no association between obesity and admission to ICU was found in COVID-19 patients aged 60 years and more [26]. In UK, out of 3883 critically ill COVID-19 patients the proportion of individuals having BMI >30 kg/m² was significantly higher as compared with the controls – individuals who were admitted to ICU due to viral pneumonia within 2017–2019. Moreover, increase in BMI was associated with growing fatality as compared with the controls [27].

As for cardiovascular disease, a nationwide analysis from China demonstrated that arterial hypertension was the commonest comorbidity (16.9%) in COVID-19 patients [28]. This was confirmed by the findings

Table 4. Lab data at the stage of hospitalization, (N = 155).

Variables	Diabetes Mellitus status						Test of difference*	
	Controls (-)			Cases (+)			Z	p-value
	Median	25 th percentile	75 th percentile	Median	25 th percentile	75 th percentile		
Hemoglobin	140.00	129.00	151.00	128.00	121.00	146.00	-1.483	0.138
Erythrocytes	4.61	4.10	5.00	4.55	4.00	5.00	-0.576	0.565
Hematocrit	39.00	36.00	43.00	39.00	36.00	44.50	-0.203	0.839
Platelets	241.00	201.50	281.50	228.50	186.50	265.00	-1.289	0.198
Leukocytes	6.30	5.30	8.00	6.00	5.30	8.00	-0.633	0.527
Stab cells	3.00	2.00	5.00	2.00	1.00	3.00	-1.763	0.078
Segmented cells	59.00	50.00	65.00	64.95	56.50	67.00	-1.276	0.202
Monocytes	6.00	4.00	8.00	4.00	1.00	6.00	-2.434	0.015
Lymphocytes	30.00	24.00	37.00	25.50	13.00	32.50	-1.918	0.055
Eosinophils	1.00	1.00	2.50	1.00	0.00	2.00	-0.863	0.388
‡ECR	10.00	5.00	17.00	15.00	5.00	25.00	-1.165	0.244
#APTT	30.50	26.15	37.50	28.90	24.80	36.00	-1.211	0.226
Prothrombin time	12.00	11.50	14.00	12.50	11.70	18.00	-1.204	0.229
Prothrombin index	85.80	80.20	100.00	82.50	73.50	90.50	-1.324	0.186
Prothrombin ratio	1.30	1.00	12.80	1.00	0.00	1.34	-1.289	0.197
International normalized ratio	1.00	1.00	1.12	1.00	1.00	1.13	-0.029	0.977
Fibrinogen	3.00	2.37	3.80	3.00	1.68	6.00	-0.011	0.991
Total protein	71.94	67.00	77.00	68.35	65.00	73.80	-1.580	0.114
Albumen	39.00	34.60	41.00	37.00	33.50	45.00	-0.146	0.884
ALT	19.00	9.00	36.00	22.20	9.00	33.00	-0.315	0.753
AST	16.30	11.55	22.95	18.00	13.00	33.00	-0.650	0.516
Total bilirubin	12.00	8.94	16.20	11.00	8.00	14.00	-0.816	0.415
Direct bilirubin	3.00	2.00	3.85	2.00	0.00	2.50	-2.205	0.207
Glucose on admission	5.00	4.50	5.70	6.00	5.00	11.00	-3.257	0.001
Glucose in [∞] ICU	8.35	5.10	10.05	22.40	16.80	28.00	-1.852	0.064
Urea	4.00	2.80	4.90	5.46	4.00	6.00	-3.316	0.001
Creatinine	69.30	56.00	82.00	66.00	54.00	98.00	-0.404	0.686
C-reactive protein	0.00	0.00	1.00	10.50	0.30	12.00	-2.378	0.017
Alpha-amylase	0.00	0.00	39.00	26.14	6.00	39.00	-1.333	0.182

‡ECR – erythrocytes sedimentation rate.

#APTT – activated partial thromboplastin time.

*Test of difference: Mann–Whitney U-test.

[∞]ICU – intensive care unit.

from Russian Federation, according to which cardiovascular disease was the most prevalent comorbidity (61.4 %) in a cohort of severely and critically ill COVID-19 patients, although its prevalence did not exceed that in the general population [25]. An Italian study reported on higher mortality among patients with cardiac disease compared with the others (36% vs. 15%) and on increased rate of thromboembolic events during

the hospitalization [29]. Besides, SARS-CoV2 is capable to directly affect cardiomyocytes leading to acute cardiac injury that is observed in 8–12 % of all COVID-19 patients and is manifested by a significant elevation of cardiac troponins. Apart from pre-existing cardiovascular disease, the appearance of acute cardiac injury contributes to worsened clinical outcomes of COVID-19 patients [30].

Table 5. Severity associated factors, (N = 155).

Variables		Diabetes Mellitus status				Test of difference	
		Controls (-)		Cases (+)		χ^2	p-value
		n	%	n	%		
Admission to ICU	No	116	94.3	21	67.7	17.795	0.000
	Yes	7	5.7	10	32.3		
Intubation	No	4	57.1	1	14.3	2.800	0.094
	Yes	3	42.9	6	85.7		
Oxygen therapy without mechanical ventilation	No	3	42.9	0	0.0	2.357	0.125
	Yes	4	57.1	4	100.0		
Number of days in [∞] ICU (median; 25 ^h and 75 ^h percentile)*		8	4; 9	5	4; 6	-1.242	0.214
Number of days on mechanical ventilation (median; 25 ^h and 75 ^h percentile)*		4	1; 6	5	4; 7	-1.150	0.250

[∞]ICU – intensive care unit.

*Test of difference: Mann–Whitney U-test.

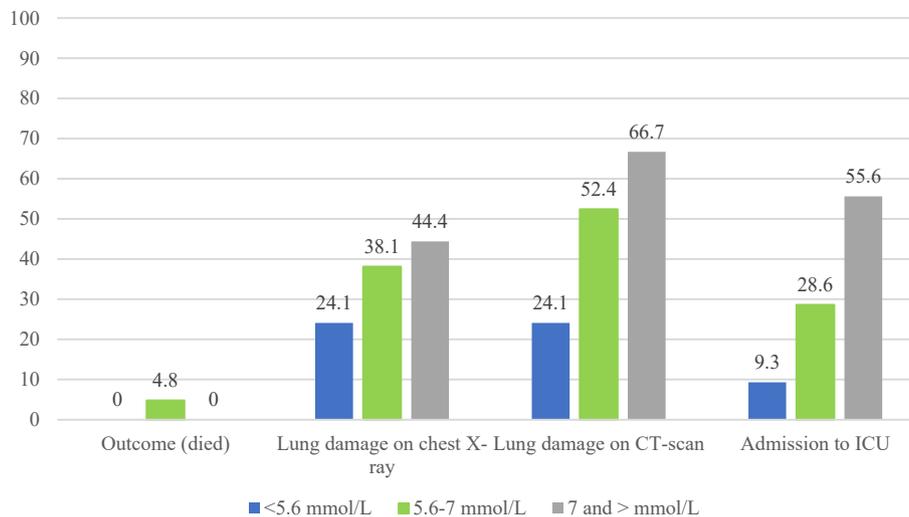


Figure 1. Outcomes and severity-associated factors in patients with different glucose levels, % (N = 155).

In fact, DM, obesity and cardiovascular disease are inter-related and thus, their effects on adverse clinical course of COVID-19 should not be considered separately. Many patients with DM also present with some type of cardiovascular disease and obesity, which could potentiate the harmful effects of each other [31]. Poorly controlled blood glucose levels, metabolic changes in DM and obesity coupled by arterial hypertension form both macrovascular and microvascular abnormalities creating a vicious cycle and further promoting adverse cardiovascular events, like thromboembolism [32]. Such, COVID-19 patients with DM and other underlying comorbidities, in particular obesity and arterial hypertension, deserve special attention and care.

Advanced age is another predictor of unfavorable outcomes in COVID-19 patients. To some degree, this could be attributed to the age-dependent decrease in immune response, which is further affected by coexisting DM [33]. Critically ill COVID-19 patients often have lymphopenia, which, aside from senile age and DM, could be explained by the destruction of lymphocytes by SARS-CoV-2, similar to what happened in case of SARS-CoV [34]. Still, this hypothesis requires further investigation. Association between lymphopenia and DM could be explained by the impairment of both innate and adaptive immunity that is frequently observed in DM [35]. Besides, vitamin D deficiency was recently hypothesized to be the independent predictor of poorer clinical outcome in COVID-19 patients. Vitamin D is needed for the production of anti-pathogenic molecules by epithelium of respiratory tract and also for regulation of inflammatory response to viral infection [36]. Kazakhstan is a Vitamin D deficient area [37] and this might be potentiated by the recent nationwide quarantine, when people were insistently advised to stay home [38]. Considering that in Kazakhstan the prevalence of pre-diabetes reaches 38.2 % and type 2 DM is up to 9.3 % in nationwide study a large group of people under the risk of developing unfavorable outcomes and complications of COVID-19 [16].

This study has several limitations. Firstly, we relied on retrospective electronic patient records, which had to be transferred manually to a unified database. To overcome this drawback, we double checked all entries into resulting database with the help of independent researcher, who inspected it and performed statistical tests for validation of data accuracy. Secondly, we did not possess the actual CTs but had to rely on their description. Thirdly, short duration of study due to which the sample size was relatively small that might influence the observations made. Fourthly, we did not have enough data to calculate BMI and to evaluate the role played by obesity as a contributing factor. Fifthly, we selected all patients on the basis of pre-diagnosed DM. Some patients who were not recognized as having DM could be excluded from the analyses.

The concentration of HbA1c was not captured which could help interpret the diabetic control status of the individual which could affect the outcome. Finally, we used a matched design, and for this we could not assess the roles of sex and age in the outcomes of COVID-19 patients with DM. A prospective study would yield a more reliable and detailed picture of the effect of DM on COVID19 patients and their outcome.

5. Conclusion

In agreement with the earlier international reports, COVID-19 patients with associated DM had less beneficial outcomes and more severe disease course both at hospital admission and final diagnosis, as compared with the age and sex-matched non-DM patients. DM was associated with not just increased lethality from COVID-19, but also with higher rates of coexisting cardiovascular pathology and kidney disease. Besides, clinical symptoms of COVID-19 and laboratory blood parameters were less favorable in DM patients in contrast with their non-DM counterparts. Obviously, there is a need to envisage early status monitoring and supportive care in this vulnerable category of patients to enable better prognosis.

Declarations

Author contribution statement

Azhar Dyusupova: Conceived and designed the experiments; Wrote the paper.

Raida Faizova: Conceived and designed the experiments.

Oksana Yurkovskaya and Tatiana Belyaeva: Performed the experiments.

Tatiana Terekhova, Amina Khismetova and Dmitry Bokov: Analyzed and interpreted the data.

Natalya Glushkova: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Antonio Sarria-Santamera: Analyzed and interpreted the data; Wrote the paper.

Alexandr Ivankov: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

- [1] M.A. Lake, What we know so far: COVID-19 current clinical knowledge and research, *Clin. Med. (Lond.)* 20 (2) (2020) 124–127.
- [2] Coronavirus Disease, 2019. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. (Accessed 24 October 2020).
- [3] C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang, P.R. Hsueh, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges, *Int. J. Antimicrob. Agents* 55 (3) (2020) 105924.
- [4] M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli, Features, Evaluation and Treatment Coronavirus (COVID-19), StatPearls Publishing, 2020.
- [5] J. Sun, et al., COVID-19: epidemiology, evolution, and cross-disciplinary perspectives, *Trends Mol. Med.* (2020).
- [6] S.P. Adhikari, et al., Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review, *Inf. Dis. Pov.* 9 (1) (17-Mar-2020) 29. BioMed Central Ltd.
- [7] Y. Semenova, N. Glushkova, L. Pivina, Z. Khismetova, Y. Zhunussov, M. Sandybaev, A. Ivankov, Epidemiological characteristics and forecast of COVID-19 outbreak in the republic of Kazakhstan, *J. Kor. Med. Sci.* 35 (24) (2020 Jun) e227.
- [8] W. Guan, et al., Comorbidity and its impact on 1590 patients with covid-19 in China: a nationwide analysis, *Eur. Respir. J.* 47 (Mar. 2020) 20005.
- [9] E. Livingston, K. Bucher, Coronavirus disease 2019 (COVID-19) in Italy, *JAMA* (2020 Mar 17).
- [10] G. Onder, G. Rezza, S. Brusaferro, Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy, *JAMA* (2020 Mar 23).
- [11] J.H. Yoo, Social distancing and lessons from Sweden's lenient strategy against corona virus disease 2019, *J. Kor. Med. Sci.* 35 (27) (2020), e250.
- [12] J.B. Kornum, R.W. Thomsen, A. Riis, H.H. Lervang, H.C. Schönheyder, H.T. Sørensen, Type 2 diabetes and pneumonia outcomes: a populationbased cohort study, *Diabetes Care* 30 (2007) 2251–2257.
- [13] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, *JAMA* 323 (2020) 1061–1069.
- [14] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, *Lancet* 395 (2020) 1054–1062.
- [15] T. Chen, D. Wu, H. Chen, et al., Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, *BMJ* 368 (2020) m1091.
- [16] N.N. Toktarova, R.B. Bazarbekova, A.K. Dosanova, The prevalence of type 2 diabetes mellitus among the adult population of Kazakhstan (results of the NOMAD registry national study), *Medicine (Almaty)* 6 (180) (2017) 43–51 [in Russian].
- [17] J.A. Lovshin, P. Bjornstad, L.E. Lovblom, et al., Atherosclerosis and microvascular complications: results from the Canadian study of longevity in type 1 diabetes, *Diabetes Care* 41 (2018) 2570–2578.
- [18] World Health Organization, Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (2019-nCoV) Infection Is Suspected: Interim Guidance [Internet], 2020. Available from, <https://apps.who.int/iris/bitstream/handle/10665/330893/WHO-nCoV-Clinical-2020%20.3-eng.pdf?sequence=51&isAllowed=5>. (Accessed 28 January 2020).
- [19] American Diabetes Association, 2. Classification and diagnosis of diabetes: standards of medical care in Diabetes2019, *Diabetes Care* 42 (Suppl. 1) (2019) S13–S28.
- [20] D.J. Drucker, Coronavirus infections and type 2 diabetes – shared pathways with therapeutic implications, *Endocr. Rev.* 41 (3) (2020 Jun 1) bnaa011.
- [21] M. Cortes Garcia, M.J. Sierra Moros, P. SantaOlalla Peralta, V. Hernandez-Barrera, R. Jimenez Garcia, I. Pachon, Clinical characteristics and outcomes of diabetic patients who were hospitalised with 2009 pandemic influenza A H1N1 infection, *J. Infect.* 64 (2012) 218–224.
- [22] G. Grasselli, A. Zangrillo, A. Zanella, et al., Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy, *JAMA* (2020 Apr 6).
- [23] Team CC-R. Preliminary estimates of the prevalence of selected underlying health conditions among patients with Coronavirus Disease 2019 - United States, February 12–March 28, 2020. *MMWR Morb. Mortal. Wkly. Rep.* 69:382–386.
- [24] C.M. Petrilli, S.A. Jones, J. Yang, et al., Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City, *medRxiv* 2004 (2020) 20057794, 2008.
- [25] P. Glybochko, V. Fomin, S. Avdeev, et al., Clinical characteristics of 1007 intensive care unit patients with SARS-CoV-2 pneumonia, *Klini ches kaya farmakologiya i terapiya = Clin Pharmacol Ther* 29 (2) (2020) 21–29 [in Russian].
- [26] J. Lighter, M. Phillips, S. Hochman, et al., Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission, *Clin. Infect. Dis.* (2020 Apr 9) ciaa415.
- [27] Audit I 2020 ICNARC report on COVID-19 in critical care, ICNARC, April 10 2020.
- [28] Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur. Respir. J.*
- [29] R.M. Inciardi, M. Adamo, L. Lupi, et al., Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy, *Eur. Heart J.* 41 (19) (2020) 1821–1829.
- [30] M. Bansal, Cardiovascular disease and COVID-19, *Diabetes Metab. Syndr.* 14 (3) (2020) 247–250.
- [31] G. Chen, F.A. McAlister, R.L. Walker, B.R. Hemmelgarn, N.R.C. Campbell, Cardiovascular outcomes in Framingham participants with diabetes: the importance of blood pressure, *Hypertension* 57 (2011) 891–897.
- [32] R.E. Climie, T.T. van Sloten, R.M. Bruno, et al., Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension, *Hypertension* 73 (2019) 1138–1149.
- [33] S.M. Opal, T.D. Girard, E.W. Ely, The immunopathogenesis of sepsis in elderly patients, *Clin. Infect. Dis.* 41 (Suppl. 7) (2005) S504–S512.
- [34] J. Gu, E. Gong, B. Zhang, et al., Multiple organ infection and the pathogenesis of SARS, *J. Exp. Med.* 202 (2005) 415–424.
- [35] L.M. Muller, K.J. Gorter, E. Hak, et al., Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus, *Clin. Infect. Dis.* 41 (2005) 281–288.
- [36] F. Mitchell, Vitamin-D and COVID-19: do deficient risk a poorer outcome? *Lancet Diab. Endocrinol.* 8 (7) (2020) 570.
- [37] O. Gromova, A. Doschanova, V. Lokshin, A. Tuletova, G. Grebennikova, L. Daniyarova, G. Kaishibayeva, T. Nurpeissova, V. Khan, Y. Semenova, A. Chibisova, N. Suzdalskaya, Z. Aitaly, N. Glushkova, Vitamin D deficiency in Kazakhstan: cross-Sectional study, *J. Steroid Biochem. Mol. Biol.* 199 (2020) 105565.
- [38] Y. Semenova, L. Pivina, Z. Khismetova, A. Auyezova, A. Nurbakyt, A. Kauysheva, D. Ospanova, G. Kuziyeva, A. Kushkarova, A. Ivankov, N. Glushkova, Anticipating the need for healthcare resources following the escalation of the COVID-19 outbreak in the republic of Kazakhstan, *J. Prev. Med. Publ. Health* 53 (6) (2020) 387–396.