Submitted: 30.11.2021
Accepted: 09.12.2021
Early publication date: 31.01.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0008
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 1/2022

Higher rate of COVID-19 mortality in patients with type 1 than type 2 diabetes: a nationwide study

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Abstract

Introduction: COVID-19 disease has a worse prognosis in patients with diabetes, but comparative data about the course of COVID-19 in patients with type 1 (T1DM) and type 2 diabetes (T2DM) are lacking. The purpose of this study was to find out the relative clinical severity and mortality of COVID-19 patients with T1DM and T2DM.

Material and methods: A nationwide retrospective cohort of patients with confirmed (PCR positive) COVID-19 infection (n = 149,671) was investigated. After exclusion of individuals with unspecified diabetes status, the adverse outcomes between patients with T1DM (n = 163), T2DM (n = 33,478) and those without diabetes (n = 115,108) were compared by using the propensity score matching method. The outcomes were hospitalization, the composite of intensive care unit (ICU) admission and/or mechanical ventilation, and mortality.

Results: The patients with T1DM had higher mortality than the age- and gender-matched patients with T2DM (n = 489) and those without diabetes (n = 489) ($p < 0.001$). After further adjustment for the HbA_{1c}, and microvascular and macrovascular complications, the odds of mortality (OR: 3.35, 95% CI: 1.41–7.96, p = 0.006) and ICU admission and/or mechanical ventilation (OR: 2.95, 95% CI: 1.28–6.77, p = 0.011) were significantly higher in patients with T1DM compared to those with T2DM. Older age (OR: 1.06, 95% CI: 1.01–1.12, p = 0.028) and lymphopaenia (OR: 5.13, 95% CI: 1.04–25.5, p = 0.045) were independently associated with mortality in patients with T1DM.

Conclusions: Patients with T1DM had worse prognosis of COVID-19 compared to T2DM patients or those without diabetes. These cases should be cared for diligently until more data become available about the causes of increased COVID-19 mortality in T1DM. **(Endokrynol Pol 2022; 73 (1): 87–95)**

Key words: *COVID-19; coronavirus; type 1 diabetes; mortality; diabetes mellitus; T1DM; Turkey*

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Introduction

Patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk of lower respiratory tract, urinary system, and skin and mucous membrane infections.[1] People with diabetes are also at increased risk of complicated influenza A (H1N1) infections, with no difference in adverse outcomes between the 2 types of diabetes [2]. As with other infectious aetiologies, certain populations, such as men, the elderly, or those with comorbid diseases, including diabetes mellitus, are more vulnerable to an unfavourable outcomes of new coronavirus disease 2019 (COVID-19) [3–7]. The frequency of T2DM among confirmed COVID-19 patients varies between 10.1% and 68.3% in different studies [8–10], and the mortality rate ranges between 8% and 60% [11–14].

Little is known about the course of COVID-19 infection in patients with T1DM rather than T2DM [15–17]. So far, only a few studies have reported the prevalence of T1DM in patients with COVID-19 infection, at between 0.6% and 2.1%, and the mortality rates range from 3% to 9%. However, these studies were too small to identify the characteristics of this vulnerable population [16, 18–20]. Moreover, potential causes of severe outcomes of COVID-19 have not been sufficiently elucidated in different settings [18–20].

This study aimed to investigate the rates of mortality, hospitalization, and admission to intensive care units (ICU) due to COVID-19 in patients with T1DM in comparison to those with T2DM and no diabetes. Moreover, we addressed the potential factors associated with poor outcomes in T1DM.

Material and methods

Study design and participants

This multi-centre retrospective cohort study was carried out using the National Electronic Database of the Turkish Ministry of Health. We identified 149,671 adult patients with a confirmed diagnosis of COVID-19 (PCR positive) between 11 March through 30 May 2020 in the database. After exclusion of individuals with unspecified diabetes status (n = 922), we classified the remaining sample as T1DM (n = 163), T2DM (n = 33478), or no diabetes (n = 115 108). To explore the relative risk of adverse outcomes in the T1DM group (see below), age- and gender-matched comparator groups were formed using the propensity score matching (PSM) method in the T2DM and no diabetes patient datasets. To increase the precision and performance of the PSM procedure, we repeated the matching by propensity scores three times in the T2DM and non-diabetic patients (Fig. 1). After the initial analyses, the PSM groups were pooled, totalling a final sample of 1141 subjects.

The design and procedures in the study are in accordance with the declaration of Helsinki and the study protocol was approved

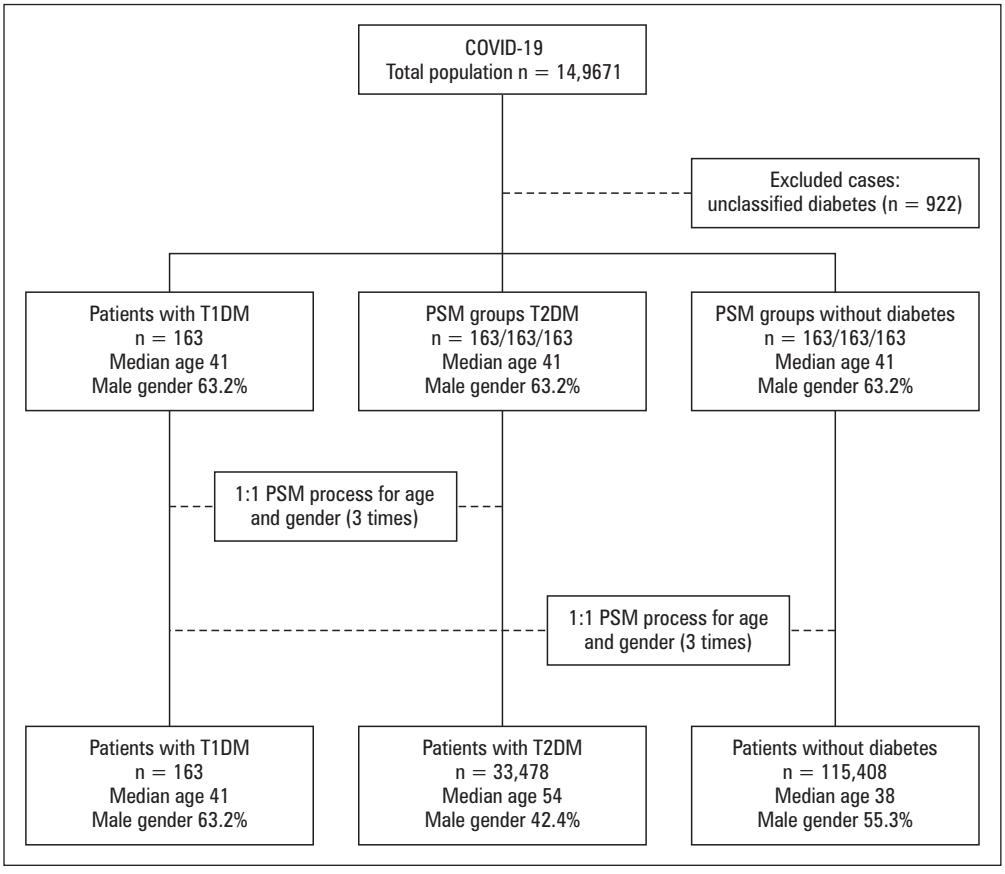

Figure 1. *Study inclusion flow chart. T1DM — type 1 diabetes mellitus; T2DM — type 2 diabetes mellitus; PSM — propensity score matching*

by the Ministry of Health Ethical Board (IRB no. 95741342–020:186404/28.10.2020).

Data collection

Sociodemographic data including age, gender, education, smoking, body mass index (BMI), comorbid diseases, and medications were recorded. The laboratory parameters obtained from the national database were blood glucose, glycosylated haemoglobin A1c (HbA_{1c} — for patients with diabetes), low-density lipoprotein cholesterol (LDL-C), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), C-reactive protein (CRP), lymphocyte count, lactate dehydrogenase (LDH), and ferritin. The tests were performed in hospital laboratories certified by the Turkish Ministry of Health. Chest computerized tomography (CT) reports were available in the national database as positive or negative for COVID-19.

Definitions

Patients with T1DM were first identified by ICD-10 codes. Each diagnosis of T1DM was further verified within the health insurance database through trace records of the patients. T2DM was defined as previously described [7] using the ICD-10 codes, or having any $HbA_{1c} \geq 6.5\%$, or monthly refill of antidiabetic medications following the diagnosis of T2DM. Undetermined records of diabetes type were considered "unclassified"; therefore, these patients were excluded from the study.

Smoking was defined as currently smoking at the time of the COVID-19 diagnosis. Higher education was described as the attained level of education for more than eight years. BMI was calculated as the ratio of weight to the square of height (kg/m^2). Hypertension, dyslipidaemia, chronic obstructive pulmonary disease (COPD), asthma, heart failure, coronary artery disease, peripheral artery disease, and cerebrovascular disease were identified using the ICD-10 codes. The composite of coronary artery disease, peripheral artery disease, and cerebrovascular disease was recorded as cardiovascular disease (CVD). Obesity was defined as BMI $\geq$ 30 kg/m^2. Chronic kidney disease was specified as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 using the CKD-EPI equation [21]. Renin–angiotensin system (RAS) medication use was composed of receiving any angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with/without their combination forms.

Outcomes

The primary outcome was mortality due to COVID-19 in patients with T1DM, compared with patients with T2DM and patients without diabetes. The secondary outcomes were hospitalization and the composite of ICU admission and/or mechanical ventilation.

Statistical analyses

Numerical data were expressed as median (interquartile range-IQR) and categorical variables as count (n) and percentage (%). Normality of distribution was assessed using the Kolmogorov-Smirnov test. Differences between groups were assessed using the chi-square test for categorical variables and Student's t-test or the Mann-Whitney U test, as appropriate.

Confirmed T1DM patients (n = 163) in the full dataset were matched using the propensity score on a scale of 1:1 by age and gender to patients with T2DM and patients without diabetes. Univariate analyses were performed to evaluate the potential variables associated with mortality, hospitalization, and ICU admission/mechanical ventilation in patients with T1DM and presented as odds ratio (OR) and its 95% confidence interval (CI). Multivariable logistic regression analysis was used to study the independent predictors of the three outcomes. Variables with significant univariate association with the outcomes and variables, which could be potential predictors despite the lack of significant univariate association, were included in a multivariate model. The Hosmer-Lemeshow test and likelihood ratio test were used to assess final model fitting. Statistical significance was defined as two-sided p values ≤0.05. Kaplan-Meier survival curves were plotted to visualize the difference between 30-day mortality rates of T1DM and PSM control groups. All data were analysed using SPSS Statistics for Windows version 25.0 (SPSS Inc. 111 Chicago, IL).

Results

Basic characteristics

Demographic and clinical variables in the overall, unmatched sample are shown in Table 1. Of the total sample of 149,671 patients with confirmed COVID-19 disease, 0.1% (n = 163) had T1DM, 22.4% had T2DM (n = 33,478), and 76.9% had no diabetes (n = 115,108). The median (IQR) age of patients with T1DM was lower than that of patients with T2DM but higher than that of patients without diabetes ($p < 0.05$ for all). There was a male predominance among patients with T1DM (63.2%) and non-diabetics (55.3%), whereas fewer patients were male among patients with T2DM (42.4%) (Fig. 1 and Tab. 1). The group with T1DM had more chronic kidney disease and coronary heart disease compared to both the T2DM and no-diabetes groups; a higher rate of microvascular and macrovascular complications than patients with T2DM; and a higher rate of hypertension, dyslipidaemia, and asthma/COPD than the no-diabetes groups ($p < 0.05$ for all) (Tab. 1). The blood glucose level at admission, the proportion of above normal LDH and ferritin, and the proportion of lymphopaenia were also higher in the group with T1DM compared to the T2DM and no-diabetes groups ($p < 0.05$) (Tab. 1). The proportion of patients using antihyperglycaemic drugs was similar in the groups with T1DM and T2DM, except for insulin therapy. The use of RAS blockers, statins, and acetyl salicylic acid was higher in both diabetes groups than in the no-diabetes group.

After matching the T1DM group (n = 163) with three different groups of patients with T2DM and patients without diabetes, the final sample consisted of 1141 individuals, of whom 14.2% had T1DM, 42.9% had T2DM (n = 489, 163 subjects in each of three PSM groups), and 42.9% had no diabetes (n = 489, 163 subjects in each of 3 PSM groups). The median (IQR) age of the sample was 41 (36) years, and 63.2% of patients were male (Fig. 1 and Tab. 2). The comparison of demographic and clinical variables after matching is shown in Table 2. The prevalence of hypertension, heart failure, chronic kidney disease, and coronary artery disease was higher when compared to patients with T2DM and those without diabetes ($p < 0.05$ for all). The microvascular and macrovascular complications were more common in patients with T1DM when compared to those with T2DM, and the rates of dyslipidaemia and asthma/COPD were higher than in the no-diabetes group ($p < 0.001$ for all). Increased blood glucose level on admission and lymphopaenia

Table 1. *Basic characteristics and comparison of clinical and demographic parameters of COVID-19 patients with type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and no-diabetes patients (crude analysis, before PSM)*

	T1DM (n = 163)	T2DM (n = 33,478)	No-diabetes (n = 115,108)	p1	p2
Age, years, median (IQR)	41 (36)	54 (81)	38 (21)	**< 0.001**	**< 0.001**
Gender, male, n (%)	103 (63.2)	14209 (42.4)	63703 (55.3)	**< 0.001**	**0.044**
Smoking (current smoker — n,%)	29 (25.7)	3612 (16.2)	18914 (22.3)	**0.006**	0.397
Follow-up centre, n (%)					
Public hospitals	118 (72.4)	25216 (75.3)	92361 (80.3)		
University hospitals	17 (10.4)	2596 (7.8)	6386 (5.5)		
Private centres	28 (17.2)	5664 (16.9)	16342 (14.2)	0.431	**0.010**
Education (9 years and over — n,%)	10 (43.5)	1309 (27.9)	6642 (39.4)	0.098	0.690
Comorbid conditions					
Hypertension, n (%)	110 (67.5)	22897 (68.4)	28497 (24.8)	0.803	**< 0.001**
Dyslipidaemia, n (%)	80 (49.1)	14923 (44.6)	8371 (7.3)	0.248	**< 0.001**
Obesity, n (%)	5 (18.5)	2112 (49.5)	2136 (21.0)	**0.001**	0.755
Asthma/COPD, n (%)	57 (35.0	11112 (33.2)	18222 (15.8)	0.631	**< 0.001**
Chronic kidney disease, n (%)	43 (54.4)	2187 (18.8)	1605 (7.7)	**< 0.001**	**< 0.001**
Coronary artery disease (CAD), n (%)	65 (39.9)	10778 (32.2)	9488 (8.2)	**0.036**	**< 0.001**
Cancer, n (%)	8 (4.9)	2402 (7.2)	2954 (2.6)	0.263	0.059
Microvascular complications, n (%)	77 (47.2)	6120 (18.3)	NA	**< 0.001**	NA
Macrovascular complications, n (%)	73 (44.8)	11864 (35.4)	NA	**0.013**	NA
Laboratory values					
CT findings of COVID-19	60 (39.0)	10900 (34.5)	22281 (21.1)	0.251	**< 0.001**
Glucose [mg/dL] median (IQR)	188 (124)	127 (78)	103 (188)	**< 0.001**	**< 0.001**
HbA_{1c} (%), median (IQR)	8.5 (3.1)	7 (2.4)	NA	**< 0.001**	NA
HbA_{1c} [mmol/mol], median (IQR)	69.4 (33.6)	53 (26.2)	NA	**< 0.001**	NA
LDL-C [mg/dL], median (IQR)	117 (71)	116 (53)	112 (52)	0.566	0.871
eGFR [mL/min/1.73 m^2], median (IQR)	58 (94)	96.4 (46)	108 (43)	**< 0.001**	**< 0.001**
AST > ULN, n (%)	8 (20)	1061 (21.1)	1685 (17.0)	0.866	0.611
ALT > ULN, n (%)	2 (4.5)	1048 (20.6)	1947 (19.6)	**0.009**	**0.012**
CRP > ULN, n (%)	52 (76.5)	6460 (70.0)	10638 (56.9)	0.244	**0.001**
Lactate dehydrogenase > ULN, n (%)	20 (62.5)	2348 (44.2)	3019 (33.4)	**0.038**	**0.001**
Ferritin > 100 ng/mL, n (%)	36 (85.7)	3016 (60.7)	3798 (49.6)	**0.001**	**< 0.001**
Lymphopenia, Lym# < 1000, n (%)	31 (32.0)	3810 (19.9)	8704 (15.7)	**0.003**	**< 0.001**
Treatments					
RAS blocker, n (%)	78 (47.9)	15746 (47.0)	13889 (12.1)	0.834	**< 0.001**
Insulin, n (%)	163 (100)	7705 (23.0)	0	**< 0.001**	NA
Statin, n (%)	51 (31.3)	8648 (25.8)	3047 (2.6)	0.112	**< 0.001**
Acetylsalicylic acid, n (%)	58 (35.6)	10219 (30.5)	8721 (7.6)	0.162	**< 0.001**
Outcomes					
Hospitalization, n (%)	99 (60.7)	18621 (55.6)	44648 (38.8)	0.190	**< 0.001**
ICU admission and intubation, n (%)	31 (31.6)	3832 (20.6)	4371 (9.8)	**0.007**	**< 0.001**
Mortality, n (%)	26 (16.0)	2565 (7.7)	2095 (1.8)	**< 0.001**	**< 0.001**

p1: T1DM *vs.* T2DM; p2: T1DM *vs.* no diabetes; COPD — chronic obstructive pulmonary disease; CT — computerized tomography; HbA_{1c} — glycosylated haemoglobin A_{1c}; LDL-C — low-density lipoprotein cholesterol; eGFR — estimated glomerular filtration rate; AST — aspartate aminotransferase; ALT — alanine aminotransferase; CRP — C-reactive protein; ULN — upper limit of normal; RAS — renin-angiotensin-aldosterone system; PSM — prospensity score matching; ICU — intensive care unit

Table 2. *Comparison of demographic and clinical parameters among COVID-19 patients with type 1 (T1DM), type 2 (T2DM) diabetes mellitus, and no-diabetes patients*

	T1DM n = 163	T2DM n = 489 (pooled PSM)	No-diabetes n = 489 (pooled PSM)	p1	p2
Age [years], median (IQR)	41 (36)	41 (36)	41 (36)	1.000	1.000
Gender, male, n (%)	103 (63.2)	309 (63.2)	309 (63.2)	1.000	1.000
Smoking (current smoker — n,%)	29 (25.7)	71 (20.1)	76 (21.5)	0.236	0.363
Follow-up centre, n (%)					
Public hospitals	118 (72.4)	367 (75.1)	406 (83.0)		
University hospitals	17 (10.4)	33 (6.7)	21 (4.3)	0.309	**0.003**
Private centres	28 (17.2)	89 (18.2)	62 (12.7)		
Education (9 years and over — n,%)	10 (43.5)	24 (31.2)	12 (20.7)	0.199	**0.038**
Comorbid conditions					
Hypertension, n (%)	110 (67.5)	286 (58.5)	170 (34.8)	**0.025**	**< 0.001**
Dyslipidaemia, n (%)	80 (49.1)	222 (45.4)	52 (10.6)	0.234	**< 0.001**
Obesity, n (%)	5 (18.5)	31 (43.7)	11 (30.6)	**0.017**	0.383
Asthma/COPD, n (%)	57 (35.0)	140 (28.6)	88 (18)	0.140	**< 0.001**
Hearth failure, n (%)	38 (23.3)	46 (9.4)	16 (3.3)	**< 0.001**	**< 0.001**
Chronic kidney disease, n (%)	43 (54.4)	40 (22.0)	14 (13.1)	**< 0.001**	**< 0.001**
Coronary artery disease (CAD), n (%)	65 (39.9)	135 (27.6)	79 (16.2)	**0.003**	**< 0.001**
Microvascular complications, n (%)	77 (47.2)	90 (18.4)	NA	**< 0.001**	NA
Macrovascular complications, n (%)	73 (44.8)	151 (30.9)	NA	**0.001**	NA
Cancer, n (%)	8 (4.9)	31 (6.3)	16 (3.3)	0.505	0.337
Laboratory values					
CT findings of COVID-19	60 (39.0)	153 (33.5)	110 (24.2)	0.217	**< 0.001**
Glucose [mg/dL], median (IQR)	188.5 (124)	139 (62)	107 (26)	**0.001**	**< 0.001**
HbA_{1c} (%), median (IQR)	8.5 (3.1)	6.6 (2.5)	NA	**< 0.001**	NA
HbA_{1c} [mmol/mol], median (IQR)	69.4 (33.6)	48.2 (27.3)	NA	**< 0.001**	NA
LDL-C [mg/dL], median (IQR)	117 (72)	109 (46)	110 (58)	0.694	0.664
eGFR [mL/min/1.73 m^2], median (IQR)	58 (94)	99 (59)	98 (49)	**< 0.001**	**< 0.001**
AST > ULN, n (%)	8 (20)	15 (19.2)	8 (14.8)	0.920	0.584
ALT > ULN, n (%)	2 (4.5)	22 (27.8)	7 (13.7)	**0.002**	0.170
CRP > ULN, n (%)	52 (76.5)	96 (75.0)	48 (54.5)	0.820	**0.005**
Lactate dehydrogenase > ULN, n (%)	20 (62.5)	41 (51.9)	22 (43.1)	0.309	0.086
Ferritin > 100 ng/mL, n (%)	36 (85.7)	47 (58.8)	31 (67.4)	**0.002**	0.050
Lymphopaenia, Lym# < 1000, n (%)	31 (32.0)	53 (20.1)	44 (16.5)	**0.018**	**0.001**
Treatments					
RAS blocker, n (%)	78 (47.9)	192 (39.3)	112 (22.9)	0.054	**< 0.001**
Insulin, n (%)	163 (100)	152 (31.1)	0	**< 0.001**	NA
Statin, n (%)	51 (31.3)	127 (26.0)	30 (6.1)	0.187	**< 0.001**
Acetylsalicylic acid, n (%)	58 (35.6)	154 (31.5)	75 (15.3)	0.334	**< 0.001**
Outcomes					
Hospitalization, n (%)	99 (60.7)	263 (53.8)	230 (47.0)	0.122	**0.002**
ICU admission and intubation, n (%)	31 (31.6)	60 (22.8)	25 (10.9)	0.086	**< 0.001**
Mortality, n (%)	26 (16.0)	34 (7.0)	14 (2.9)	**0.001**	**< 0.001**

p1: T1DM *vs.* T2DM; p2: T1DM *vs.* no diabetes; COPD — chronic obstructive pulmonary disease; CT — computerized tomography; HbA_{1c} — glycosylated haemoglobin A_{1c}; LDL-C — low-density lipoprotein cholesterol; eGFR — estimated glomerular filtration rate; AST — aspartate aminotransferase; ALT — alanine aminotransferase; CRP — C-reactive protein; ULN — upper limit of normal; RAS — renin–angiotensin–aldosterone system; ICU — intensive care unit

were also more prevalent in the group with T1DM than among patients with T2DM and those without diabetes ($p < 0.05$) (Tab. 2). Similar to the crude comparisons, the proportion of patients using antihyperglycaemic medications, except for insulin, therapy was similar in the groups with T1DM and T2DM after matching. The use of RAS blockers, statins, and acetyl salicylic acid use was higher in both diabetes groups compared with the no-diabetes group in matched analysis.

Outcome analysis

A comparison of study outcomes between unmatched groups showed a significantly higher rate of mortality, hospitalization, and the composite of ICU admission and/or mechanical ventilation in patients with T1DM compared to patients without diabetes ($p < 0.001$ for all) (Tab. 1). The rates of mortality and ICU admission and/or mechanical ventilation were also higher than in the T2DM group ($p < 0.05$).

Considering the pooled PSM groups, there was a greater risk of mortality in the T1DM group than in the T2DM groups ($p < 0.001$). No significant difference was observed between the T1DM and T2DM groups regarding hospitalization or ICU admission and/or mechanical ventilation. On the other hand, the risk of mortality, hospitalization, and ICU admission and/or mechanical ventilation in the group with T1DM was higher in comparison to the no-diabetes groups ($p < 0.01$ for all) (Tab. 2). The comparison of outcomes across each PSM group is given in Supplementary File — Table 1.

After further adjustment for the HbA_{1c}, microvascular, and macrovascular complications, the odds of mortality (OR: 3.35, 95% CI: 1.41–7.96, $p = 0.006$) and ICU admission and/or mechanical ventilation (OR: 2.95, 95% CI: 1.28–6.77, $p = 0.011$) were significantly higher in patients with T1DM compared to the group with T2DM (Fig. 2). The odds of mortality (OR: 6.44, 95% CI: 3.27–12.67, $p < 0.001$), hospitalization (OR: 1.74, 95% CI: 1.21–2.50, $p = 0.003$), and ICU admission and/or mechanical ventilation (OR: 3.78, 95% CI: 2.08–6.84, $p < 0.001$) were also significantly higher in patients with T1DM compared to the no-diabetes group.

Predictors of outcomes

Multivariate logistic regression analyses showed that older age (OR: 1.06, 95% CI: 1.01–1.12, $p = 0.028$) and lymphopaenia (OR: 5.13, 95% CI: 1.04–25.5, $p = 0.045$) were independently associated with mortality in patients with T1DM. Chest CT findings of COVID-19 (OR: 4.41, 95% CI: 1.12–17.3, $p = 0.033$) were associated with an increased risk of hospitalization, while older age (OR: 1.05, 95% CI: 1.01–1.10, $p = 0.016$) was associated with a higher risk of ICU admission (Supplementary File — Tab. S2).

The survival curves

The Kaplan-Meier curves showing the cumulative survival rates of 30-day mortality are displayed for the crude analysis in Figure 3A and matched analysis in Figure 3B. Both analyses yielded lower survival rates for patients with T1DM (logrank test $p < 0.001$).

Discussion

The results of this nationwide retrospective observational cohort study showed a significantly higher risk of hospitalization, ICU admission/intubation, and mortality in patients with T1DM than in patients without diabetes. Also, the results revealed that patients with T1DM have an approximately three-fold higher risk of ICU admission/mechanical ventilation and mortality when compared to patients with T2DM. The risk remained higher even after the results were adjusted for age, gender, and microvascular and macrovascular complications. To our knowledge, this is one of the most comprehensive studies published so far on T1DM patients with COVID-19.

There are several studies in the literature showing the relationship between COVID-19 disease and T2DM. Most of these studies reported that COVID-19 disease

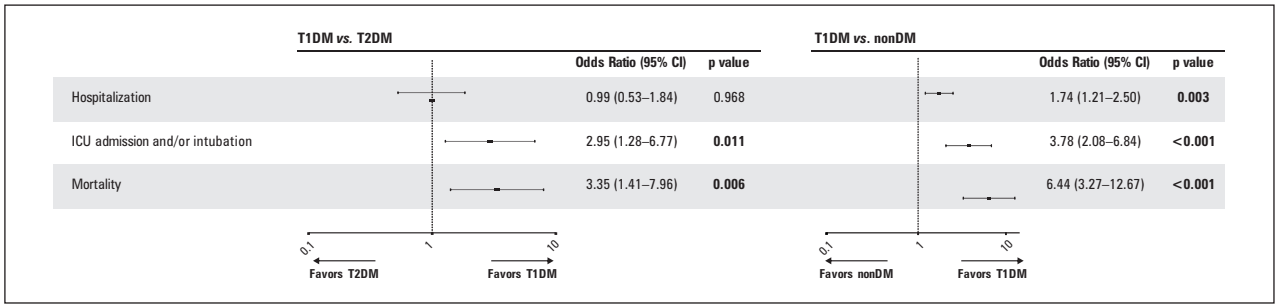

Figure 2. *The risks of COVID-19 outcomes in patients with type 1 diabetes mellitus (T1DM) relative to type 2 diabetes mellitus (T2DM) and non-diabetics; ICU — intensive care units*

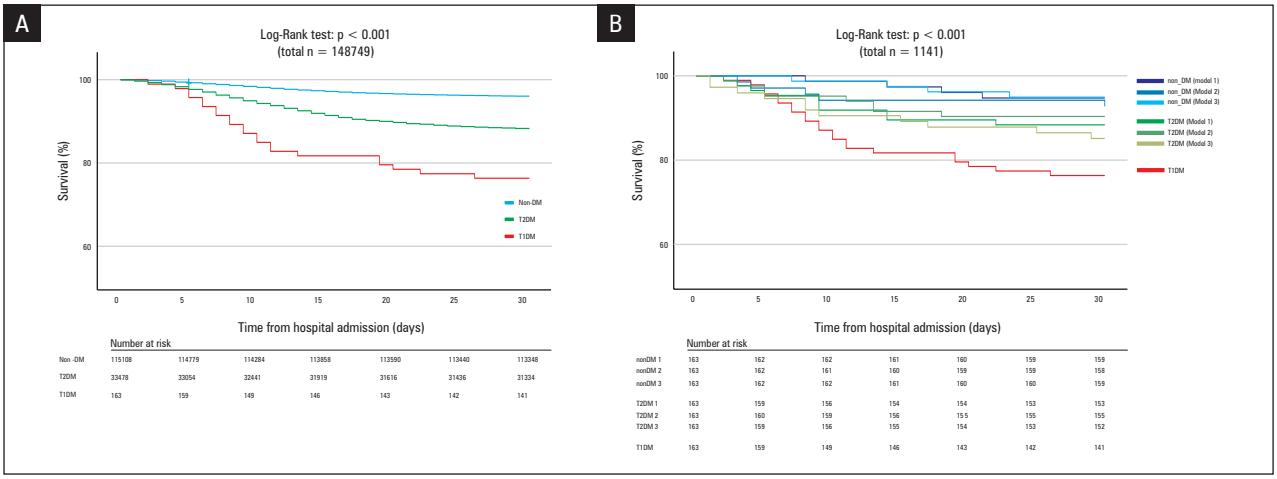

Figure 3. *Kaplan-Meier survival curves showing crude (**A**) and propensity score matching (PSM) scenarios (**B**)*

is quite common among T2DM patients, and generally with a more complicated course [5–7]. Very few studies have been published on COVID-19 in patients with T1DM; however, similar findings to T2DM have been reported [15–17, 19, 22, 23]. The low prevalence of T1DM in the general population, the relatively younger age of T1DM patients compared to T2DM patients, and the fact that the COVID-19 pandemic, at least at the beginning, affects older patients rather than younger ones are among the proposed reasons for the scarcity of data on T1DM [24, 25].

We observed a 16% overall mortality rate in COVID-19 patients with T1DM. Compared to the 1.8% mortality in the population without diabetes in the same dataset, such an increased risk deserves special attention because it seems to be one of the highest numbers reported studies so far. A whole-population study from England reported a 3.5% death rate among T1DM patients [16, 20]. The rate of mortality in the CORONADO study was 5.4% [23], while a recent UK study reported a 27% death rate in COVID-19 patients [22]. A multicentre and another small-scale study from the United States reported 9% and 3% death rates, respectively [17, 18]. Higher mortality of patients with T1DM in our study may be explained by the increased burden of comorbidities. In a national registry from England, patients with T1DM who died due to COVID-19 had markedly higher rates of comorbidities including cardiovascular or renal comorbidities by 62.3%, heart failure by 23.9%, and stroke by 11.0% [20]. T1DM patients in our study had a more severe comorbidity burden, such as coronary artery disease, chronic kidney disease, and heart failure, by 39.9%, 54.4%, and 23.3%, respectively. Almost half of these patients had at least one microvascular complication.

In addition to the mortality outcome, the risk of hospitalization in the present study seems to be one of the highest among similar publications in the literature. Overall, six out of ten patients with T1DM in our study were hospitalized following COVID-19 diagnosis. Previous studies from different countries reported the hospitalization rates in patients with T1DM between 21.9% and 51%. Also, almost one-third of our patients were admitted to the ICU, which was recorded as 5% to 35% in other studies from different countries [17, 22, 25, 26]. In the CORONADO study, 19.6% of patients with T1DM required mechanical ventilation [23]. Not surprisingly, the risk of a more severe COVID-19 course was higher in the T1DM population with a higher burden of significant comorbidities.

The present study compared T1DM and T2DM patients in terms of mortality and other prognostic factors using three different PSM models. In all models, the mortality rate was significantly higher in patients with T1DM, while there was no significant difference in the hospitalization, ICU admission, and intubation rates. Few studies so far have compared patients with T1DM and T2DM in terms of COVID-19 severity and mortality. One study reported fewer deaths in patients with T1DM compared to patients with T2DM (5.4% *vs.* 10.6%), although the analysis was limited to 56 patients with T1DM [23]. In addition, there were significant differences in age and gender between the T1DM and T2DM groups. Another study from the UK reported that the odds of mortality from COVID-19 was 3.5 times higher in patients with T1DM and 2.0 times higher in those with T2DM relative to patients without diabetes [16]. In our three PSM models, the T1DM and T2DM groups were matched for age and gender, and the median age in both groups was 41 years. Although the data on the duration of diabetes duration was not available in our study, it is well-known that it is typically longer in individuals with T1DM than in those with T2DM of the same age because the onset of diabetes is

much earlier in T1DM. Thus, one major reason for the increased mortality in patients with TIDM might be the longer duration of diabetes. Also, the median HbA_{1c} level in patients with T1DM in the present study was significantly higher than in the patients with T2DM. The risk of mortality from COVID-19 was reported to be higher at markedly increased HbA_{1c} levels in both T1DM and T2DM in a recent study from England [20]. Therefore, poor glycaemic control may also be involved in the mechanism of increased mortality in our study. For this reason, we conducted a further comparison of age, gender, HbA_{1c} levels, and microvascular and macrovascular complications between the matched groups of T1DM and T2DM. The results showed that patients with T1DM had higher mortality rates independently of HbA_{1c} levels and complications. These findings suggest that T1DM and T2DM are completely different diseases, and different immune dysfunctions in patients with T1DM may induce higher mortality rates in these patient groups.

Numerous studies have repeatedly identified older age as a significant factor in the course of COVID-19, not only in T2DM [27–29] but also in T1DM [16, 20, 25]. Our findings are consistent with the earlier findings that in COVID-19 patients with T1DM, age is a strong predictor of mortality and poor prognosis as well. Likewise, we identified lymphopaenia as a predictor of worse prognosis in the T1DM group, which is in line with the previous reports from others [7, 30, 31]. In this regard, T1DM patients with older age and lymphopaenia should be treated more carefully during COVID-19.

Several limitations of the present study should be acknowledged. First, its observational design precludes establishing a causal relationship between the type of diabetes and outcomes. Second, all patients included in the study had a confirmed diagnosis of COVID-19 (PCR positive). The lack of symptomatic but unconfirmed COVID-19 cases or patients with false-negative COVID-19 PCR results may reduce the generalizability of our findings. Third, some data were unavailable in the dataset, such as duration of diabetes and insulin doses, which could be important factors to predict prognosis. And finally, the low number of patients with T1DM can be considered as a limitation. One major strength of this study is its population-based, nationwide design. Also, to our knowledge, this study is one of the most comprehensive reports of COVID-19 outcomes in adult patients with T1DM.

Conclusion

COVID-19 patients with T1DM have higher mortality rates than patients with T2DM and those without diabetes. The increased mortality risk in patients with T1DM appears to be independent of age, gender, glycaemic control, and complications, suggesting that T1DM and T2DM have different pathophysiological mechanisms. Therefore, patients with T1DM seem to be particularly disadvantaged during the COVID-19 pandemic, suggesting some prioritization needs for prevention and care.

Acknowledgements

The authors gratefully acknowledge the Turkish healthcare professionals who worked hard for the management of COVID-19 sufferers during the outbreak and collected these data. We convey our deepest respect and gratitude to the memories of all our colleagues who lost their lives during the pandemic.

Data availability

The datasets generated during the current study are secured in a network and are not open to public sharing. The outputs can be copied following analysis but not the core patient registry. Practically, if requested in the future for any reason, additional information can be retrieved from the registry by contacting the corresponding author on reasonable request.

Author contributions

I.D., A.S., I.S., and I.T. were involved in the conceptualization and methodology of the study. N.A., O.C., M.C. and S.B. were responsible for the data download and verification. I.D., C.H., and I.T. performed the formal analysis and investigation. I.T., A.S., A.A., R.E., and I.S. critically reviewed and edited the first draft. All the authors were involved in the writing of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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