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ORIGINAL ARTICLE

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Clinical characteristics and outcomes of COVID-19 in patients with type 2 diabetes in Turkey: A nationwide study (TurCoviDia)

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has been reported to be associated with a more severe course in patients with type 2 diabetes mellitus (T2DM). However, severe adverse outcomes are not recorded in all patients. In this study, we assessed disease outcomes in patients with and without T2DM hospitalized for COVID-19.

Methods: A nationwide retrospective cohort of patients with T2DM hospitalized with confirmed COVID-19 infection from 11 March to 30 May 2020 in the Turkish Ministry of Health database was investigated. Multivariate modeling

was used to assess the independent predictors of demographic and clinical characteristics with mortality, length of hospital stay, and intensive care unit (ICU) admission and/or mechanical ventilation.

Results: A total of 18 426 inpatients (median age [interquartile range, IQR]: 61 [17] years; males: 43.3%) were investigated. Patients with T2DM (n = 9213) were compared with a group without diabetes (n = 9213) that were matched using the propensity scores for age and gender. Compared with the group without T2DM, 30-day mortality following hospitalization was higher in patients with T2DM (13.6% vs 8.7%; hazard ratio 1.75; 95% CI, 1.58-1.93; $P < .001$). The independent associates of mortality were older age, male gender, obesity, insulin treatment, low lymphocyte count, and pulmonary involvement on admission. Older age, low lymphocyte values, and pulmonary involvement at baseline were independently associated with longer hospital stay and/or ICU admission.

Conclusions: The current study from the Turkish national health care database showed that patients with T2DM hospitalized for COVID-19 are at increased risk of mortality, longer hospital stay, and ICU admission.

KEYWORDS

COVID-19, hospital stay, intensive care unit admission, mortality, type 2 diabetes

Highlights

- Coronavirus disease 2019 (COVID-19) takes an unfavorable course in patients with type 2 diabetes mellitus (T2DM), and the risk increases in individuals with certain conditions, some of which are not modifiable.
- This study showed significantly higher mortality due to COVID-19 in hospitalized patients with T2DM than without (13.6% vs 8.7%; hazard ratio 1.75; 95% CI, 1.58-1.93).
- Older age, male gender, obesity, preexisting insulin treatment, low lymphocyte count, and pulmonary involvement on admission were the significant associates of COVID-19 mortality.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused higher rates of morbidity and mortality in certain patient populations.[1-3] Type 2 diabetes mellitus (T2DM) is another growing pandemic of recent decades with serious health outcomes.[4,5] The coalescence of the two pandemics makes patients with diabetes more vulnerable to the consequences of COVID-19 infection.[6-8]

Many patients with T2DM have comorbidities like cardiovascular disease (CVD), renal disease, and other complications that have a significant impact on overall disease course and outcomes.[9,10] Moreover, the COVID-19 pandemic has led to reduced amounts of physical activity,[11] which may be linked not only to the public restrictions to keep social distancing but also to the fear of being infected.[12] Consequently, a sedentary lifestyle is typically associated with a deterioration in glycemic control.[13] Available data from different territories and countries around the world have indicated that not all patients with diabetes have the same risk of mortality due to COVID-19 infection.[14-16] Therefore, there is a need for identifying the most vulnerable phenotype of patients with T2DM to improve the current standard of acute care and follow-up.

The increasing prevalence of diabetes mellitus is a significant health issue in Turkey,[17] which brings the country to the top of the European region.[18] More admissions of people with diabetes mellitus with COVID-19 to health care facilities can potentially increase the challenges in health care provision during the pandemic. In this

study, using the largest nationwide patient registry, we aimed to investigate the clinical characteristics and outcomes of people with or without T2DM hospitalized for COVID-19. We also aimed to analyze the potential factors associated with adverse study outcomes among patients with T2DM.

2 | METHODS

2.1 | Study design and participants

The TurCoviDia is a multicenter, retrospective cohort study, generated from the Turkish Ministry of Health National Electronic Database. Since more than 95% of the population in Turkey have only public health insurance coverage, the information extracted from this database represents all seven geographical regions accounting for a population of 84 million. The design and procedures in the study are in accordance with the declaration of Helsinki and the study protocol was approved by the Ministry of Health Ethical Board (95741342-020/27112019).

There were 149 671 adult patients with a confirmed diagnosis of COVID-19 (polymerase chain reaction [PCR] positive) between 11 March through May 2020 in the database. We excluded subjects who received outpatient care (n = 85 317), patients with type 1 DM (n = 370), and those unclassified for the diagnosis of DM (n = 715). In the remaining population, there were 18 621 inpatients with T2DM diagnosis screened using the *International*

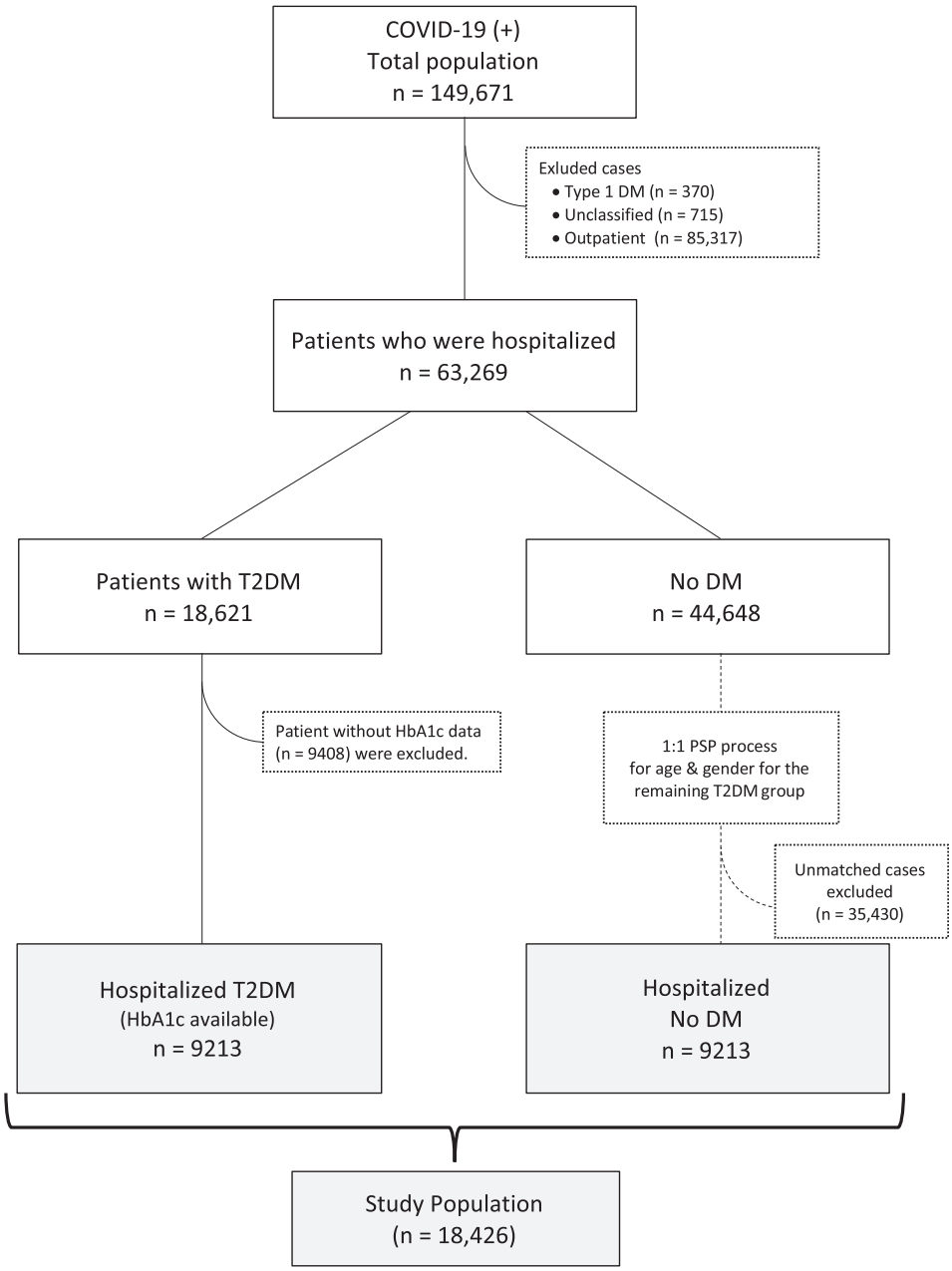

FIGURE 1 Study inclusion flow chart

TABLE 1 Basic characteristics of patients with and without T2DM hospitalized for COVID-19

	T2DM (n = 9213)	No T2DM (n = 9213)	Available data (n) (T2DM/no T2DM)	*P*
Age, years (median [IQR])	61 (17)	61 (17)	9213/9213	1.000
Gender (male), n (%)	3990 (43.3)	3990 (43.3)	9213/9213	1.000
Smoking (current smoker), n (%)	768 (12.5)	932 (15.1)	6125/6186	**<.001**
Follow-up center, n (%)				
Public hospitals	7118 (77.3)	7239 (78.6)		
University hospitals	718 (7.8)	665 (7.2)	9213/9212	.090
Private centers	1377 (14.9)	1308 (14.2)		
Education (9 years and over), n (%)	243 (17.2)	239 (17.5)	1410/1363	.834
BMI, kg/m^2 (median [IQR])	30.7 (6.74)	28.2 (6.36)	1590/928	**<.001**
Clinical severity				
Prolonged hospital stay (>8 days), n (%)	3978 (50.0)	4064 (48.3)	7963/8410	**.037**
ICU admission, n (%)	2065 (22.5)	1477 (16.1)	9189/9196	**<.001**
Prolonged ICU stay (>6 days), n (%)	1076 (52.3)	767 (52.2)	2056/1469	.943
Intubation, n (%)	1400 (15.2)	918 (10.0)	9189/9196	**<.001**
Death, n (%)	1250 (13.6)	803 (8.7)	9213/9213	**<.001**
Chest CT on admission consistent with COVID-19, n (%)	4450 (48.4)	4196 (45.6)	9189/9196	**<.001**
Laboratory values				
Glucose, mg/dL (median [IQR])	153 (100)	108 (28)	1708/1263	**<.001**
HbA1c, % (median [IQR])	7.1 (2.50)	-	9213/-	**NA**
HbA1c, mmol/mol (median [IQR])	54 (4)	-	9213/-	**NA**
HbA1c >7% (53 mmol/mol), n (%)	4949 (53.7)	-	9213/-	**NA**
Total cholesterol, mg/dL (median [IQR])	190 (62)	191 (75)	1117/423	.426
Triglycerides, mg/dL (median [IQR])	147 (102)	123 (86)	1556/566	**<.001**
HDL-C, mg/dL (median [IQR])	44 (17)	46 (19)	1235/464	**.009**
LDL-C, mg/dL (median [IQR])	113 (52)	115 (64)	1240/427	.217
eGFR, mL/min/1.73 m^2 (median [IQR])	78 (41.4)	82.7 (35.4)	3827/2707	**<.001**
eGFR <15, n (%)	178 (3.8)	62 (1.9)	4652/3284	**<.001**
eGFR 15-30, n (%)	180 (3.9)	78 (2.4)	4652/3284	**<.001**
eGFR 30-60, n (%)	776 (16.7)	430 (13.1)	4652/3284	**<.001**
eGFR >60, n (%)	3521 (75.7)	2714 (82.6)	4652/3284	**<.001**
AST >ULN, n (%)	441 (22.2)	350 (21.9)	1990/1597	.871
ALT >ULN, n (%)	380 (18.9)	292 (18.3)	2013/1597	.667
D-dimer >ULN, n (%)	658 (60.7)	476 (56.8)	1084/838	.085
CRP >ULN, n (%)	2668 (77.5)	1888 (71.7)	3444/2633	**<.001**
Procalcitonin >ULN, n (%)	115 (17.0)	60 (13.7)	678/437	.148
Lactate dehydrogenase >ULN, n (%)	1043 (49.6)	708 (47.6)	2102/1487	.236
Ferritin >100 ng/mL, n (%)	1446 (68.2)	831 (66.0)	2120/1259	.187
Fibrinogen >ULN, n (%)	243 (77.6)	176 (74.9)	313/235	.454
Lymphopenia, Lym# <1000, n (%)	1875 (29.8)	1897 (31.0)	6286/6113	.145
Comorbid conditions				
Hypertension, n (%)	7948 (86.3)	5741 (62.3)	9213/9213	**<.001**

TABLE 1 (Continued)

	T2DM (n = 9213)	No T2DM (n = 9213)	Available data (n) (T2DM/no T2DM)	P
Dyslipidemia, n (%)	5992 (64.3)	1643 (17.8)	9213/9213	**<.001**
Obesity, n (%)	870 (54.8)	344 (37.1)	1589/927	**<.001**
Asthma/COPD, n (%)	3756 (40.8)	2766 (30.0)	9213/9213	**<.001**
Heart failure, n (%)	1353 (14.7)	613 (6.7)	9213/9213	**<.001**
Coronary heart disease, n (%)	4362 (47.3)	2524 (27.4)	9213/9213	**<.001**
Peripheral artery disease, n (%)	1011 (11.0)	490 (5.3)	9213/9213	**<.001**
Cerebrovascular disease, n (%)	461 (5.0)	249 (2.7)	9213/9213	**<.001**
Retinopathy, n (%)	455 (4.9)	-	9213/-	
Neuropathy, n (%)	2241 (24.3)	-	9213/-	
Chronic kidney disease, n (%)	1131 (24.3)	570 (17.4)	4652/3284	**<.001**
Cancer, n (%)	843 (9.2)	617 (6.7)	9213/9213	**<.001**
Treatments				
Insulin-based regimen, n (%)	3670 (39.8)	-	9213/-	-
RAS blocker, n (%)	6183 (67.1)	3639 (39.5)	9213/9213	**<.001**
Statin, n (%)	4044 (43.9)	882 (9.6)	9213/9213	**<.001**
Acetylsalicylic acid, n (%)	4188 (45.5)	2212 (24.0)	9213/9213	**<.001**

Note: p values in bold are significant at <0.05.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ICU, intensive care unit; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lym#, lymphocyte count; NA, not applicable; RAS, renin-angiotensin system; T2DM, type 2 diabetes mellitus; ULN, upper limits of normal.

Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes and 44 648 inpatients without T2DM diagnosis. Patients with a T2DM diagnosis without any glycosylated hemoglobin (HbA1c) measurement within the past 12 months (n = 9408) were excluded. The remaining patient group with T2DM (n = 9213) was included in the final analyses. Using the propensity score matching approach, a comparator group without T2DM (n = 9213) was created from the sample of 44 648 inpatients (Figure 1).

2.2 | Data collection

Sociodemographic characteristics (gender, age, body mass index [BMI], smoking, and education), comorbid diseases, macrovascular complications, microvascular complications, and medications were recorded. Laboratory test results available in the collected dataset were blood glucose, HbA1c, lipid parameters (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol, and triglycerides), creatinine, liver function tests (aspartate aminotransferase and alanine aminotransferase), C-reactive protein (CRP), lymphocyte count, procalcitonin, lactate dehydrogenase, ferritin, fibrinogen, and D-dimer. These tests were from the hospital laboratories certified by the Turkish Ministry of Health. Chest computed tomography (CT) results were available as positive or negative for COVID-19.

2.3 | Definitions

Smoking was defined as currently smoking at the time of the COVID-19 diagnosis. Higher education was defined as the attained education level of more than 8 years. BMI was calculated as the ratio of weight to the square of height (kg/m^2). T2DM was defined based on the ICD-10 codes or having an HbA1c ≥6.5%, or monthly refill of antidiabetic medications following the diagnosis of T2DM. Hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), asthma, heart failure, coronary artery disease, peripheral artery disease, and cerebrovascular disease were defined based on the ICD-10 codes. The last three morbidities were defined as CVD. Obesity was defined as BMI ≥30 kg/m^2.

Diabetic retinopathy was defined as having an intravitreal injection or laser photocoagulation in addition to an ICD-10 code for T2DM. Diabetic neuropathy diagnosis was based on the ICD-10 codes of diabetic neuropathy with the prescription of pregabalin, gabapentin, duloxetine, or alpha-lipoic acid. Chronic kidney disease was defined as a

TABLE 2 Comparison of clinical and demographical characteristics of patients with T2DM according to mortality

	Nonsurvivors (n = 1250)	Survivors (n = 7963)	*P*
Age, years (median [IQR])	71 (14)	60 (16)	**<.001**
Gender (male), n (%)	685 (54.8)	3305 (41.5)	**<.001**
Smoking (current smoker), n (%)	75 (13.3)	693 (12.5)	<.556
Follow-up center, n (%)			
Public hospitals	834 (66.7)	6284 (78.9)	
University hospitals	120 (9.6)	598 (7.5)	**<.001**
Private centers	296 (23.7)	1081 (13.6)	
Education (9 years and over), n (%)	23 (13.9)	220 (17.7)	.220
BMI, kg/m^2 (median [IQR])	30.5 (7.3)	30.8 (6.7)	<.706
Chest CT on admission consistent with COVID-19, n (%)	633 (51.6)	3817 (47.9)	**<.016**
Laboratory values			
Glucose, mg/dL (median [IQR])	170 (103)	151 (99)	**.004**
HbA1c, % (median [IQR])	7.2 (2.6)	7.1 (2.5)	**.033**
HbA1c, mmol/mol (median [IQR])	55.4 (28.4)	54.1 (27.3)	**.033**
HbA1c >7% (53 mmol/mol), n (%)	688 (55.1)	4076 (51.3)	**.012**
Total cholesterol, mg/dL (median [IQR])	178 (68)	191 (62)	.191
Triglycerides, mg/dL (median [IQR])	142 (85)	147 (103)	.338
HDL-C, mg/dL (median [IQR])	44 (20)	44 (17)	.917
LDL-C, mg/dL (median [IQR])	103 (62)	113 (52)	.206
eGFR, mL/min/1.73 m^2 (median [IQR])	53.6 (49.3)	80.6 (37.6)	**<.001**
AST >ULN, n (%)	115 (39.0)	326 (19.2)	**<.001**
ALT >ULN, n (%)	43 (14.9)	337 (19.5)	.061
D-dimer >ULN, n (%)	152 (83.1)	506 (56.2)	**<.001**
CRP >ULN, n (%)	433 (93.7)	2235 (74.9)	**<.001**
Procalcitonin >ULN, n (%)	65 (36.5)	50 (10)	**<.001**
Lactate dehydrogenase >ULN, n (%)	242 (77.1)	801 (44.8)	**<.001**
Ferritin >100 ng/mL, n (%)	273 (88.3)	1173 (64.8)	**<.001**
Fibrinogen >ULN, n (%)	48 (85.7)	195 (75.9)	.109
Lymphopenia, Lym# <1000, n (%)	410 (50.7)	1028 (18.8)	**<.001**
Comorbid conditions			
Hypertension, n (%)	1179 (94.3)	6769 (85.0)	**<.001**
Dyslipidemia, n (%)	866 (69.3)	5056 (63.5)	**<.001**
Obesity, n (%)	97 (55.4)	773 (54.8)	.942
Asthma/COPD, n (%)	620 (49.6)	3136 (39.4)	**<.001**
Heart failure, n (%)	402 (32.2)	951 (11.9)	**<.001**
Coronary heart disease, n (%)	821 (65.7)	3541 (44.5)	**<.001**
Peripheral artery disease, n (%)	210 (16.8)	801 (10.1)	**<.001**
Cerebrovascular disease, n (%)	125 (10.0)	336 (4.2)	**<.001**
Retinopathy, n (%)	115 (9.2)	340 (4.3)	**<.001**
Neuropathy, n (%)	339 (27.1)	1902 (23.9)	**.013**
Chronic kidney disease, n (%)	296 (52.7)	835 (20.4)	**<.001**
Cancer, n (%)	196 (15.7)	647 (8.1)	**<.001**

TABLE 2 (Continued)

	Nonsurvivors (n = 1250)	Survivors (n = 7963)	*P*
Treatments			
Insulin-based regimen, n (%)	763 (61.0)	2907 (36.5)	**<.001**
RAS blocker, n (%)	1007 (80.6)	5176 (65.0)	**<.001**
Statin, n (%)	625 (50.0)	3419 (42.9)	**<.001**
Acetylsalicylic acid, n (%)	773 (61.8)	3415 (42.9)	**<.001**

Note: p values in bold are significant at <0.05.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lym#, lymphocyte count; RAS, renin-angiotensin system; T2DM, type 2 diabetes mellitus; ULN, upper limits of normal.

TABLE 3 Multivariate associates of prolonged hospital stay (>8 days), ICU admission/mechanical ventilation, and mortality in patients with T2DM

	Prolonged hospital stay (>8 days)		ICU admission/mechanical ventilation		Mortality	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.04 (1.02-1.06)	**<.001**	1.07 (1.05-1.10)	**<.001**	1.09 (1.05-1.13)	**<.001**
Gender (male)	-	-	-	-	2.68 (1.33-5.40)	**.006**
Obesity	-	-	-	-	2.36 (1.18-4.74)	**.016**
Insulin-based regimen	-	-	-	-	3.48 (1.62-7.45)	**.001**
CT findings of COVID-19	1.54 (1.06-2.24)	**.023**	1.69 (1.05-2.70)	**.030**	2.25 (1.18-4.30)	**.013**
Lymphopenia (Lym# < 1000/μL)	2.24 (1.42-3.53)	**.001**	1.87 (1.13-3.10)	**.015**	2.37 (1.26-4.47)	**.007**

Note: Variables included in the multivariate analyses were age, gender, glycosylated hemoglobin >7%, pulmonary CT findings of COVID-19, hypertension, dyslipidemia, obesity, asthma/chronic obstructive pulmonary disease, heart failure, cardiovascular disease, chronic kidney disease, cancer, lymphopenia, insulin-based regimens, renin-angiotensin system blockers ± combinations, statins, acetylsalicylic acid (only significant associates are given in the table).
p values in bold are significant at <0.05.

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; Lym#, lymphocyte count; OR, odds ratio; T2DM, type 2 diabetes mellitus.

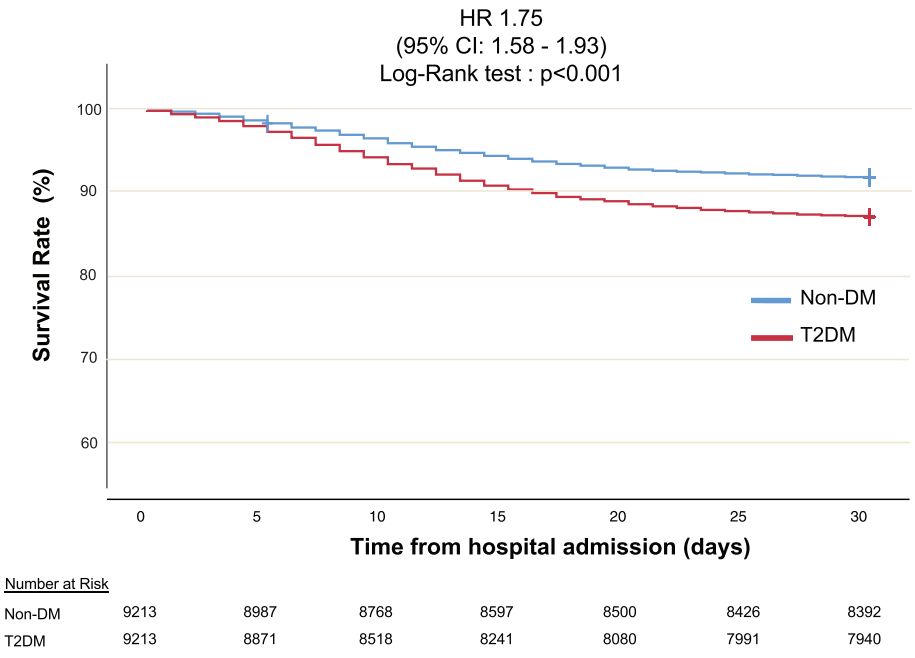

FIGURE 2 30-day mortality in hospitalized patients with and without T2DM

decreased estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[19] Insulin-based regimens were defined as receiving any insulin regimen with/without oral antidiabetic drugs. Renin-angiotensin system (RAS) blocker use was defined as receiving any angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with/without their combination forms.

2.4 | Study outcomes

The primary outcome was mortality or live discharge at any point during hospitalization. The secondary outcomes were the length of hospital stay and the composite of intensive care unit (ICU) admission or mechanical ventilation during hospitalization.

2.5 | Statistical analyses

Numerical data were expressed as median (interquartile range, IQR) and categorical variables as counts (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 the Student *t* test or the Mann-Whitney *U* test, as appropriate.

Hospitalized T2DM patients (n = 9213) of the full dataset were matched using the propensity score on a scale of 1:1 by age and gender to individuals in a COVID-19 (+) control group of hospitalized patients without T2DM. Kaplan-Meier survival curves were plotted to study the association between T2DM diagnosis and mortality and component outcomes. Univariate analyses were performed to evaluate the potential variables associated with mortality, length of hospital stay, and ICU admission/mechanical ventilation in the T2DM group and presented by odds ratio (OR) and its 95% CI. Multivariable logistic regression analysis was used to study the independently associated 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. Stratified multivariable-adjusted analyses were performed according to age (<65 years or ≥65 years) and gender. The Hosmer-Lemeshow test and likelihood ratio test were used to assess final model fitting. Statistical significance was defined as two-sided *P* values ≤.05. All data were statistically analyzed using SPSS Statistics for Windows 25.0 (SPSS Inc, Chicago, Illinois).

3 | RESULTS

The sociodemographic and clinical characteristics of the total sample (N = 18 426; median age [IQR]: 61 [17] years; males: 43.3%), the T2DM group (n = 9213), and age- and gender-matched controls (n = 9213) are displayed in Table 1. Smoking was less frequent (12.5% vs 15.1%, $P < .001$) and the median BMI was higher (30.7 kg/m^2 vs 28.2 kg/m^2, $P < .001$) in patients with T2DM. The median length of hospital stay and ICU stay was 8 and 6 days, respectively, in the whole sample. The rate of prolonged hospital stays (>8 days) ($P = .037$), ICU admission, intubation, and death ($P < .001$ for all) were significantly higher in patients with T2DM. CT findings on admission consistent with COVID-19 pulmonary involvement were significantly higher in patients with T2DM ($P < .001$). Hypertension, dyslipidemia, obesity, chronic pulmonary diseases (COPD/asthma), heart failure, coronary artery, peripheral artery and cerebrovascular diseases, chronic kidney disease, and cancer were significantly more prevalent in the T2DM group ($P < .001$). The use of RAS blockers, statins, and acetylsalicylic acid was also significantly more common in patients with T2DM ($P < .001$). On admission, CRP, glucose, and triglyceride levels were higher ($P < .001$) in the T2DM group, whereas HDL-C ($P = .009$) and eGFR values ($P < .001$) were lower.

As stated above, subjects who were coded as T2DM in the database without HbA1c records were excluded from the analyses (n = 9408). The demographic and clinical characteristics of this sample were compared with those of the nondiabetic patients, again using the propensity scores on a scale of 1:1 by age and gender. The clinical outcomes in this sample were also significantly poorer than the age- and gender-matched patients with COVID-19 without DM (Table S1).

The comparison of the clinical and demographical characteristics of patients with T2DM was performed according to mortality. The nonsurvivors were significantly older, predominantly male, with higher rates of pulmonary involvement, lymphopenia, hypertension, dyslipidemia, asthma/COPD, heart failure, CVD, retinopathy, neuropathy, chronic kidney disease, cancer, and were more on insulin-based regimens, RAS blockers, statins, and acetylsalicylic acid therapy ($P < .001$) (Table 2).

3.1 | Multivariate analyses in patients with T2DM

The multivariable logistic regression analysis revealed age, positive CT findings of COVID-19, and lymphopenia as the independent associates of prolonged hospital stay (>8 days) and the composite of ICU admission and

intubation. In the multivariable model, age, male gender, positive CT findings of COVID-19, lymphopenia, obesity, and the use of insulin-based regimens were significantly associated with mortality (Table 3).

3.2 | Survival analysis

The Kaplan-Meier graph of 30-day mortality curves in the total sample is given in Figure 2. During a median follow-up of 11 days, the rate of mortality in patients with T2DM (13.6%) vs nondiabetic patients (8.7%) was significantly different (OR 1.75; 95% CI, 1.58-1.93; $P < .001$).

4 | DISCUSSION

TurCoviDia is the first nationwide report of adult patients with T2DM hospitalized for COVID-19 in Turkey. The results showed that the risk of death, longer length of hospital stay, and ICU admission is significantly higher in patients with T2DM. Older age, obesity, being on any insulin treatment, lymphopenia, and pulmonary findings on CT consistent with COVID-19 were associated with reduced survival in the present study.

To the best of our knowledge, this is the largest study on a population of hospitalized COVID-19 patients with T2DM published so far. Various studies from different territories and countries of the world have reported different mortality rates ranging from 8% to 60% in COVID-19 patients with T2DM.[6,15,16,20,21] The mortality rate of 13.6% in the current study is one of the lowest rates so far reported. In this regard, the inconsistencies between the present and previous findings may be explained by the single-center design and small patient numbers in the former studies, which decrease the generalizability of the results to the global population. Moreover, overloading the health care system during the pandemic may influence the general demographic and clinical characteristics of hospitalized patients in different health care systems.[6,15,16,20,21] Concerning the period of mortality, some authors have reported the event rates only for the first several days,[15] while others reported for longer periods of up to 4 weeks[21] or the entire hospitalization duration.[16] We assessed the mortality outcome during the total hospitalization period. One important factor potentially related to lower mortality in the present study may be that the Turkish health care system did not face significant overloading during the early period of the pandemic. Moreover, universal coverage of the national health insurance system and the early use of the standard inpatient protocols set by the National Scientific Advisory Committee during the pandemic might have led to lower mortality events in this study.

The demographic and clinical features of the current study sample can be said to reflect the characteristics of the Turkish patients with T2DM, as reported in a recently published nationwide survey, the TEMD Study.[22] The age and gender distributions, BMI, HbA1c, LDL-C levels, and smoking rates of the patients are very similar to those of the TEMD study. However, we recorded numerically higher rates of hypertension, coronary artery disease, and chronic kidney disease, which may not be surprising as the current sample consisted of hospitalized patients, while the former study enrolled participants from the outpatient setting. The most vulnerable phenotype for mortality we observed in patients with T2DM was older age, male gender, obesity, insulin treatment, lymphopenia on admission, and the CT findings showing pulmonary involvement. Many of these determinants of mortality were also reported in other studies for patients with diabetes.[6,7,16,23] Notwithstanding, there may be some differences between our findings and the previous reports owing to the heterogeneity of the patient population, inclusion criteria, social coverage, and national COVID-19 management policies.

The impact of age, gender, and BMI on mortality has been consistently addressed by different authors.[1,16,24-26] The vulnerability of older adults to COVID-19 infection has been linked to decreased innate and adaptive immune responses and aggravated inflammatory cytokine productions, described as a process of immunosenescence.[27] Why males have a worse disease course has not been understood so far. Gender-specific modulation of the genes encoding for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry receptors, sex hormone-driven innate and adaptive immune responses, or the effect of gender-specific lifestyle, psychological stress, and socioeconomic conditions have all been proposed in the mechanism of gender-specific consequences of COVID-19.[28,29] The susceptibility of people with obesity to the worse clinical outcomes of COVID-19 is not new and can be explained by several mechanisms including impaired respiratory functions, higher levels of pro-inflammatory status, and a higher risk of thrombosis.[30] Obesity can also increase insulin resistance and impair glycemic regulation in patients with T2DM.

Despite a univariate association of HbA1c>7% to the mortality outcome, poor glycemic control was not an independent predictor of adverse outcomes in our adjusted analyses. Preclinical data about the mechanistic links between glucose control and Middle East respiratory syndrome coronavirus (MERS-CoV) infection[31] and the effect of long-term glycemic control on the clinical outcomes of the COVID-19-infected subjects with T2DM[21] suggest that poorer glycemic control can increase the risk of worse health outcomes. However, HbA1c level was not shown to be associated with the clinical outcomes in COVID-19 patients with diabetes in other studies.[15,16,23] More data are

required in this context; however, it may be postulated that other variables such as age, male gender, obesity, and insulin treatment might have a more significant impact on mortality than HbA1c level. Moreover, that the role of insulin treatment is a significant determinant of mortality rather than the HbA1c levels can be interpreted as the duration of diabetes and disease burden being more important than the glycemic regulation to predict mortality in COVID-19 patients with T2DM. This causality in insulin-treated individuals has been addressed by different authors.[16,32]

Hypertension has been reported as a significant predictor of worse clinical outcomes in several reports of COVID-19 patients.[33,34] However, we did not observe a significant association between hypertension and the study outcomes in patients with T2DM. On the other hand, there is significant heterogeneity between the published reports regarding the effect of hypertension on the outcomes of patients with diabetes.[6] The impact of preexisting hypertension on COVID-19-related mortality has not been consistently observed in studies with a large number of patients with T2DM.[15,16,23] The magnitude of the effect of hypertension on the COVID-19 outcomes is likely determined by the additional comorbidities in patients with diabetes. More data are required to understand the interrelation of hypertension, antihypertensive drugs, and the course of COVID-19 in the general population and patients with T2DM.

There are several limitations to the current study. Some of the clinical data such as arterial blood pressures or oxygen saturation were not available in the dataset. As hospitalized patients with COVID-19 infection were studied, it may not be possible to extrapolate the results to all the people with T2DM having less severe clinical forms of COVID-19 infection who were not hospitalized. The strengths of this study include the large sample size representative of the whole country, comparison of the group with T2DM with a well-matched nondiabetic group, and the inclusion of patients with confirmed PCR tests admitted to all types of care facilities including secondary and tertiary care centers, private or government hospitals, or university hospitals. Also, the hospitalized patients during the pandemic were uniformly treated in accordance with the guidance of the National Scientific Advisory Committee for COVID-19.

In conclusion, the TurCoviDia study showed that patients with T2DM hospitalized for COVID-19 had an increased risk of mortality, longer hospital stay, and higher rates of ICU admission compared with patients without DM. Older age, male gender, obesity, insulin treatment, lymphopenia, and pneumonia findings on CT were the predictors of adverse outcomes among patients with T2DM.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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