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RESEARCH ARTICLE

Risk factors predicting hospital length of stay in older patients with type 2 diabetes with Covid-19

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Abstract

Background Patients with Covid-19 disease could present with flu-like symptoms. However, nearly half of the subjects with positive test results for Covid-19 remain asymptomatic. Data on factors related to the duration of hospital stay in Covid-19 patients with diabetes mellitus remain limited.

Objective We aimed to identify risk factors predicting prolonged hospital length of stay (LOS) among diabetic patients hospitalized with Covid-19.

Methods This cohort study involved patients with type 2 diabetes (T2D) admitted to a tertiary hospital with mild or moderate Covid-19 between August 1 and November 31, 2020. Data on demographics, laboratory parameters, and clinical treatments were extracted from the medical records. Prolonged LOS was defined as equal to or greater than the median hospitable stay time. We used univariate and multivariate logistic regression analyses to explore risk factors associated with LOS.

Results We included 87 hospitalized T2D patients with mild or moderate Covid-19. The mean age was 69.5 ± 6.9 years, and 59.8% were female. In the unadjusted analysis, factors influencing the length of hospitalization were as follows: undertreatment of diabetes, high procalcitonin level, glycated hemoglobin, and low lymphocyte count. After adjustment for all covariates, subjects with a low lymphocyte had a 3.9 fold increased risk of prolonged LOS (OR:3.925 CI:1.044–14.755 p = 0.043).

Conclusions A lower lymphocyte count on admission was associated with prolonged hospital LOS in older T2D patients with Covid-19, suggesting this marker could help clinicians predict complications for an adverse outcome.

Keywords Covid-19 · Diabetes Mellitus · Inflammation · Lymphocyte count · Length of hospital stay · Older adults · Pandemic

Introduction

Diabetes mellitus (DM) is a risk factor for serious infectious diseases including coronavirus disease-19 (Covid-19) which increases health care expenditures and decreases the quality of life, even resulting in mortality [1]. The majority of patients with Covid-19 disease only present with mild flu-like symptoms [2]. However, nearly half of the subjects with positive test results for Covid-19 remain asymptomatic [2]. On the other hand, older adults with type 2 diabetes (T2D) may experience severe illness and these patients are particularly susceptible to severe complications of Covid-19 [3, 4]. Although the reasons behind older adults with T2D being at higher risk of adverse outcomes due to Covid-19 are not fully understood, recent studies have suggested that chronic hyperglycemia-induced inflammatory and immune imbalance may play an important role in this association [5, 6].

Because the Covid-19 pandemic has brought challenges to public health services, hospital length of stay (LOS) is critical for managing high patient volumes [7]. Optimizing hospital stay preserves access to care related to non-Covid-19 to maintain the healthcare system [8, 9]. However, LOS for Covid-19 patients is variable due to subject characteristics,

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course of the disease, and care practices. Importantly, identification of prolonged hospital stay may allow physicians to reevaluate critical patients, focusing on the delivery of specific interventions, and improving the efficiency of hospital care [10, 11].

In recent studies, particular attention has been paid to patients with T2D infected by Covid-19, whose LOS may be much longer [12]. Accordingly, a recent cohort study emphasized that the risk of developing severe Covid-19 and prolonged LOS was substantially higher in patients with T2D than in the healthy population [13]. On the other hand, it could be argued that patients with T2D with non-severe Covid-19 have increased risk factors for prolonged LOS [14]. A recent retrospective cohort study of 58 patients with non-severe Covid-19 only weak evidence for an association between diabetes mellitus and prolonged LOS [15]. Therefore, particularly in these populations, the risk factors for prolonged LOS should be evaluated in detail [15]. However, there is little evidence on the prognostic factors of DM associated with an extension of hospitalization in non-severe illnesses due to Covid-19 [12]. For example, in patients with T2D, being able to predict whether someone with a non-serious Covid-19 will be hospitalized for a long or short time can guide care decisions and result in individualized decisions about the management of their comorbidities and their risk of complications [16, 17]. Therefore, it is crucial to determine the most vulnerable patients with diabetes mellitus, even if they have non-severe Covid-19 during the pandemic.

It is important to note that, inflammation is involved in the pathogenesis of Covid-19 infection and various clinical conditions. For instance, increased neutrophil and decreased lymphocyte counts (thus increased neutrophil/lymphocyte ratio) have been reported in various inflammatory conditions such as Hashimoto's disease [18], diabetes mellitus [19], and irritable bowel disease [20], and thyroid conditions [21]. Indeed, elevated neutrophil and reduced lymphocyte count have also been reported in SARS Cov2 infection [22]. We hypothesized that clinically relevant parameters may have an impact on LOS in older patients with T2D with non-severe Covid-19. Therefore, we aimed to investigate whether baseline factors on hospital admissions for Covid-19 were possible predictors of prolonged LOS in this group.

Methods

Study design and patients

We conducted a secondary analysis using data from a prospective cohort study of patients aged 60 years and older hospitalized with non-severe Covid-19 pneumonia between August 1 and November 31, 2020 in a pandemic hospital in Turkiye. The diagnosis, severity, monitoring (hospitalization or discharge), and treatment for Covid-19 were established according to the guidelines published by the Turkish Ministry of Health's Scientific Committee for Covid-19.

Participants were recruited based on the following criteria: (1) tested positive by RT-PCR test for SARS-CoV-2 and chest computed tomography (CT) results were positive for Covid-19 (2) having self-care ability; (3) having mild or moderate symptoms (non-severe); (4) no severe comorbidities (such as heart failure, renal failure) or mental or neurodegenerative disorders; and (5) established diagnosis of diabetes mellitus. The diagnostic criteria for non-severe Covid-19 were as follows: [1] respiratory rate ≤ 30 times/min; [2] oxygen saturation ≥ 94% at rest; and [3] $PaO_2/FiO_2 \geq 300$ mmHg [4] did not have any emergency medical reasons [respiratory failure or mechanical ventilation needed, shock, or organ failure and intensive care unit (ICU) admission needed for monitoring and treatment [23].

We included all hospitalized T2D patients according to any established diagnosis before admission or the American Diabetes Association guidelines for diagnostic criteria [24]. Patients with a history of type 1 diabetes mellitus, dementia or neurodegenerative disease (epilepsy, multiple sclerosis, Parkinson's disease, etc.), terminal illness (malignancy, advanced organ failure), severe Covid-19 infection (unstable vital signs, dyspnea, tachypnea, SpO2 <%94 while on oxygen therapy, mechanical ventilation), and death during hospitalization were excluded.

The study was approved by the research ethics committee of the hospital (Nu: 2020 – 374), and informed consent was obtained before admission to the current study. All data were kept confidential and had no personal identifiers.

Endpoint

The endpoint of this study was hospital length of stay (LOS), which was calculated according to the number of days of hospitalization. Patients were divided into two groups according to the median LOS value: ≤ 7 days as normal and > 7 days as prolonged LOS.

Data collection and other variables

All patients underwent comprehensive geriatric assessment immediately upon admission to the hospital. Additionally, a basic laboratory investigation was performed within 24 h of admission. During hospitalization, patients received supportive usual care including oral and intravenous medications, according to the current guidelines. Patients meeting

the following criteria were discharged: (1) having a normal body temperature for three consecutive days; (2) no significant respiratory symptoms; (3) significant improvement of pneumonia; and (4) no complications of Covid-19 (e.g., delirium, stroke, venous thromboembolism, acute cardiac events or acute liver or renal injury).

Table 1 Characteristics of patients

Parameters	Total (n = 87)	Length of Hospital Stay		*p* value
		≤ 7 days (n = 41)	**> 7 days (n = 46)**	
Age (years), mean + SD	69.5 ± 6.9	69.9 ± 7.6	69.2 ± 6.3	0.67
Gender (Female), N (%)	52 (59.8)	26 (63.4)	26 (56.5)	0.51
Comorbidities, N (%)				
Diabetes Mellitus Complex	52 (59.8)	24 (58.5)	28 (60.9)	0.82
Healthy	35 (40.2)	17 (41.5)	18 (39.1)	
Hypertension	71 (82.6)	34 (82.9)	37 (82.2)	0.93
Cardiovascular disease	22 (25.3)	6 (14.6)	16 (34.8)	**0.031**
COPD	15 (17.2)	6 (14.6)	9 (19.6)	0.54
Charlson Comorbidity index, mean + SD	2.7 ± 1.0	2.6 ± 0.9	2.8 ± 1.1	0.52
Laboratuary parameters, N (%) or mean + SD				
Neutrophil, ($< 4 * 10^9$/L)	33 (37.9)	14 (34.1)	19 (41.3)	0.49
Lymphocyte, ($< 1 * 10^9$/L)	35 (40.2)	12 (29.3)	23 (50.0)	**0.049**
Hemoglobin, (< 12 g/dl)	38 (43.7)	15 (36.6)	23 (50.0)	0.20
Platelet, ($< 150 * 10^9$/L)	22 (25.3)	8 (19.5)	14 (30.4)	0.24
Ferritin, (> 500 ml/ng)	11 (17.2)	4 (17.4)	7 (17.1)	0.97
CRP, (> 30 mg/L)	64 (73.6)	27 (65.9)	37 (80.4)	0.12
Fasting glucose, mg/dl	200.4 ± 97.1	190.1 ± 99.6	209.3 ± 94.9	0.36
Glycated hemoglobin, (%)	8.2 ± 1.8	7.8 ± 1.8	8.5 ± 1.7	**0.048**
AST, (> 35 IU/L)	26 (29.9)	10 (24.4)	16 (34.8)	0.29
Procalcitonin, (> 0.05 ng/ml)	50 (57.4)	17 (41.4)	33 (71.7)	**0.024**
Diabetes Medications, N (%)				
Metformin	63 (72.4)	31 (75.6)	32 (69.6)	0.52
Sulphonylurea	17 (19.5)	8 (19.5)	9 (19.6)	0.99
DPP-4 inhibitors	31 (35.6)	13 (31.7)	18 (39.1)	0.47
SGLT-2 inhibitors	12 (13.8)	4 (9.8)	8 (17.4)	0.30
Insulin	38 (43.7)	15 (36.6)	23 (50.0)	0.20
Treatment, N (%)				
Overtreatment	16 (18.4)	10 (24.4)	6 (13.0)	0.17
Undertreatment	39 (44.8)	12 (29.3)	27 (58.7)	**0.006**
Optimal treatment	32 (36.8)	19 (46.3)	13 (28.3)	0.08

AST, Aspartate aminotransferase; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; DPP-4 dipeptidyl peptidase-4; SGLT-2, Sodium-glucose Cotransporter-2; SD, Standart Deviation

$p < 0.05$ statistically significant

Baseline characteristics including age, sex, comorbidities (hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and others), diabetes medications (oral anti-diabetic drugs and/or insulin), and laboratory parameters within 24 h of admission [levels of white blood cell (WBC), lymphocyte neutrophil, hemoglobin (Hb), platelet, fasting glucose, glycated hemoglobin, aspartate aminotransferase (AST), C-reactive protein (CRP), ferritin, and procalcitonin] were identified using patient self-reports and electronic health records. All data were collected by two fellow geriatricians who were trained and supervised by the same clinician. The Charlson-Deyo comorbidity index (CCI) was used to assess the overall comorbidity burden, which assigned a weighted sum of scores to each of 17 comorbid conditions [25].

Hospitalized T2D patients were categorized as "healthy" (few coexisting chronic illnesses, intact cognitive and functional status), "complex" (multiple coexisting chronic illnesses or 2 + instrumental activities of daily living impairments or mild-to-moderate cognitive impairment), and "very complex" (long-term care, end-stage chronic illnesses, moderate-to-severe cognitive impairment, or 2 + instrumental activities of daily living impairment dependencies) according to the American Diabetes Association (ADA) and American Geriatrics Society (AGS) guidelines [26, 27].

The definitions of the treatment status of diabetes (undertreatment, optimal treatment, or overtreatment) were derived from the ADA guidelines. HbA1c measurement at hospital admission was used as the index date. Treatment status was assessed with this index measurement below or above the target HbA1c values provided by the ADA [28–30].

Statistical analysis

The distribution of continuous variables was assessed using the Kolmogorov Smirnov test. For normally distributed variables, means with standard deviations were calculated, while medians and min-max were used to describe variables that were not normally distributed. Categorical variables were described as frequencies (percentages). Continuous variables were compared using the Student's t-test and the Mann-Whitney U test, as appropriate. Differences in categorical variables were assessed using the chi-square test. The association between the outcome variable (LOS) and each covariate was assessed using univariate analysis to obtain unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). After adjusting for confounding variables,

we conducted a multivariable logistic regression analysis to calculate adjusted ORs with 95% CIs. These variables were chosen according to their relationship with the outcome or > 10% effect estimate changes. The model fit of the prediction model was assessed by computing the Hosmer-Lemeshow goodness-of-fit test. The effect size was measured using the Cox and Snell R^2, and Nagelkerke R^2. All statistical analyses were performed using the SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). For all statistical tests, a two-tailed *p*-value less than 0.05 was considered statistically significant.

Results

Patients characteristics

We included a total of 87 hospitalized T2D patients with non-severe Covid-19. The mean age of all participants was 69.5 ± 6.9 years and 59.8% of the sample were female. Metformin (72.4%), insulin (43.7%), and DPP4 inhibitors (35.6%) were the most commonly used antidiabetic drugs. The majority of subjects (59.8%) were in the complex category of diabetes and many of them (44.8%) were undertreated. The demographic and clinical characteristics of the patients are presented in Table 1.

Patients were categorized according to their LOS. Hospital LOS was longer for patients with cardiovascular disease (p = 0.031), lower lymphocyte count (p = 0.049), higher glycated hemoglobin (p = 0.048), higher procalcitonin (p = 0.024) and undertreatment for diabetes (p = 0.006) **(**Table 1**).** There were no differences in diabetic medications **(**Table 1**).**

Factors associated with LOS

Univariate analysis demonstrated that LOS was significantly associated with undertreatment (OR = 3.43; CI:1.40–8.38; p = 0.007) and high procalcitonin (OR = 3.88; CI:1.14–13.18; p = 0.030). In addition, glycated hemoglobin and low lymphocyte count were marginally related to prolonged LOS (OR = 1.29; Cl:0.99–1.67; p = 0.053 and OR = 2.41; CI:0.99–5.86; p = 0.051) **(**Table 2**)**.

In the multivariate logistic regression analysis controlling for study confounders, only a low lymphocyte was associated with a 3.9-fold increased risk of prolonged LOS (> 7 days) (OR:3.92; Cl:1.04–14.75; p = 0.043) **(**Table 2**)**. The other variables were not statistically significant after adjustment (**Table 2**). The model explained 23.2% (Cox and Snell R^2) and 31.2% (Nagelkerke R^2) of the variance in prolonged LOS **(**Table 2**)**. The Hosmer-Lemeshow test revealed a good fit of the data with the model ($\chi 2 = 4.287$, p = 0.830).

Discussion

This study found that low lymphocyte count is an independent variable affecting LOS in older subjects with T2D with non-severe Covid-19 even after controlling for potential confounding factors. Complex health status and undertreatment for diabetes with were common. In addition, there were previously no studies examining the associations

Table 2 Predictors of prolonged length of hospital stay (> 7 days)

Variables	Univariate			Multivariate		
	OR	CI (95%)	*p*	OR	CI (95%)	*p*
Age, years	1.45	0.52–4.01	0.46	1.53	0.37–6.32	0.55
Gender (Female), Yes	1.33	0.56–3.15	0.51	1.48	0.37–5.89	0.57
DM (Complex), Yes	1.10	0.46–2.59	0.82	1.15	0.25–5.17	0.84
Undertreatment, Yes	3.43	1.40–8.38	**0.007**	3.91	0.32–46.50	0.28
Low neutrophil, ($< 4 * 10^9$/L)	1.35	0.56–3.24	0.49	-	-	-
Low lymphocyte, ($< 1 * 10^9$/L)	2.41	0.99–5.86	0.051	3.92	1.04–14.75	**0.043**
Low hemoglobin, (< 12 g/dl)	1.73	0.73–4.09	0.20	-	-	-
Low platelet, ($< 150 * 10^9$/L)	1.80	0.66–4.88	0.24	-	-	-
High ferritin, (> 500 ml/ng)	1.02	0.26–3.94	0.97	-	-	-
Fasting glucose, mg/dl	1.01	0.99–1.01	0.35	-	-	-
Glycated hemoglobin, (%)	1.29	0.99–1.67	0.053	1.21	0.63–2.35	0.55
AST, (> 35 IU/L)	1.65	0.64–4.21	0.29	-	-	-
High procalcitonin, (> 0.05 ng/ml)	3.88	1.14–13.18	**0.030**	4.42	0.93–20.98	0.06
High CRP, (> 30 mg/L)	2.13	0.80–5.64	0.12	-	-	-

AST, Aspartate aminotransferase; CI, Confidence interval; CRP, C-reactive protein; DM, Diabetes Mellitus; OR, Odds ratio

Significant variables, including age,gender, DM (complex), glycated hemoglobin, undertreatment and with *p* value < 0.1 in the univariate logistic regression model were entered as predictors of length of hospital stay in the multivariate regression model

$p < 0.05$ statistically significant

between laboratory parameters and LOS in this population. Our results show that lymphocyte count may be an important indicator for the estimation of hospital stay in older individuals with T2D infected by Covid-19, suggesting that clinicians should pay more attention to older adults with low lymphocyte count from a clinical point of view.

The disturbances in total white blood cells (e.g., leucocytosis, neutrophilia, and lymphopenia), part of the immune system, have been considered responses of immunity to the inflammation process [31]. Lymphopenia, a decrease in lymphocyte count, is a common laboratory finding in a wide variety of diseases such as diabetic kidney injury [32], frailty [33], hepatic fibrosis [34], and malignancy [35]. Additionally, cumulative evidence emphasizes that inflammation plays a crucial role in the Covid-19 course, from its initiation to the progression of viral sepsis [36, 37]. Additionally, lymphopenia was reported as a manifestation of acute Covid-19, possibly as a result of specific damage caused by the virus [36, 38]. However, further studies are needed to clarify and better understand the pathophysiological mechanism of the low lymphocyte count in patients with Covid-19.

Our clinical question in this study was the potential impact of clinical factors on LOS in hospitalized T2D patients. The findings indicate that low lymphocyte count was associated with prolonged LOS in this group. Results from two recent studies demonstrated that patients with DM had more lymphopenia and longer LOS than those without DM [39, 40]. Another study, which considered the time between the onset of symptoms and a negative RT-PCR result, found that severe Covid-19 was associated with lower lymphocyte counts in diabetic patients [40]. Unlike previous studies, we only analyzed patients with T2D at older ages to refine and improve comparisons. A possible explanation for our findings on the relationship between lymphocyte count with LOS could be that lymphopenia due to Covid-19 indeed impairs the adaptive immunity, and antiviral responses can not be effectively initiated in a process similar to that in viral sepsis [36]. Our study provides an opportunity to reveal that lymphopenia may be a potential marker for LOS in vulnerable populations with comorbid DM, but further research is still needed on this causal relationship.

The LOS of diabetic patients with Covid-19 is variable, and conflicting results have been reported. In a recent cohort study of older 76 patients with DM, the median LOS was 13 days (IQR: 9–19) [41]. Another recent observational study demonstrated that older 111 hospitalized T2D patients with Covid-19 were at a greater risk of ICU admission and had a longer LOS (median LOS = 14, (IQR: 8–25)) [39]. Although the mean LOS in our study was shorter than that in previous cohorts, it was comparable to a recent cohort with a large sample size [12]. However, a full comparison of the results was not obtained because LOS was not an outcome indicator in these studies [42, 43]. The variation in LOS by the study might be explained by different admission criteria, disease severity, types of diabetes, social coverage, heterogeneity of the patient population, and national Covid-19 management policies [13, 44–48].

DM in older adults is highly heterogeneous, and the wide spectrum of health and functional status of older adults may contribute to complexity and heterogeneity [49, 50]. Additionally, a recent study has shown that the majority of older patients with DM have complex or poor health status [51]. In line with this, this complex or poor health status through several factors including advanced age, functional capacity, comorbidities, and undertreatment makes the management of DM even more challenging during hospitalization, resulting in an increased risk of prolonged LOS [13, 52]. It is also possible that viral infections may lead to fluctuations in blood glucose levels, which may exacerbate the complications of diabetes and prolong the recovery process, especially in undertreatment patients [53–56]. However, in our study, the association between undertreatment and LOS was not significant when possible clinical and laboratory parameters were included in the multivariate analysis. More research is needed to obtain accurate results; however, it may be postulated that other variables such as advanced age, and comorbidities might have a more significant impact on LOS than treatment status [57].

The current study has some limitations. First, lymphocyte count was analyzed only at the admission inpatient clinic. Repeated lymphocyte measurements could help demonstrate a more exact inflammatory status. Second, biomarkers (IL-6, IL-8, tumor necrosis factor-alpha, etc.) were not evaluated in this research. Third, we evaluated important factors such as demographics, comorbid conditions, antidiabetic medications, and laboratory parameters; however other covariates could have influenced the length of hospital stay, including frailty, medications, duration of diabetes, and social and environmental factors [58]. Fourth, our study had a small sample size of older patients with mild or moderate Covid-19 which limits the generalizability of our findings to severe cases and the general older population. The participants in our study were very well characterized with recorded multiple covariates that may be confounders of these associations, including diabetes subgroup (complexity/healthy) and treatment status of diabetes (undertreatment/overtreatment), and adjusted for these factors in multivariable analyses. Besides, we conducted a real-world study, performed in real clinical conditions, which would facilitate potential translation of the results to routine practice for hospitalized T2D patients.

Conclusions

This study can be an important starting point for future research areas. The relationship between low lymphocyte count at hospital admission and prolonged hospital stay among hospitalized T2D patients is a remarkable result. The findings indicate that considering the lymphocyte count may be beneficial in improving the management of this group of hospitalized patients. In addition, this study reinforces the need for further research in larger cohorts to increase our knowledge of the factors affecting the hospital stay of older adults due to Covid-19, especially given the high risk of hospital complications in those with diabetes.

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Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Health Science (Date.2020/No.374).

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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