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Article

Factors Associated with Length of Hospitalization in Diabetic Patients with Mild COVID-19: Experiences from a Tertiary University Center in Serbia

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Abstract: Background. During the COVID-19 pandemic, there was an increased number of the hospitalized COVID-19 positive patients suffering from type 2 diabetes mellitus (T2DM). The objective of this research was to explore factors associated with the length of hospitalization of patients with T2DM and mild form of COVID-19. Material and Methods. This retrospective cohort study involved all patients who tested positive for COVID-19 and were treated in the dedicated COVID department of the University Clinical Center (UCC) in Nis between September 10, 2021, and December 31, 2021. Upon admission, patients underwent blood tests for biochemical analysis, including blood count, kidney and liver function parameters (C-reactive protein-CRP, creatinine kinase, D-dimer), as well as glycemia and HbA1c assessments. Additionally, all patients underwent lung radiography. Univariate and multivariate regression analyses were employed to assess the impact of specific factors on the length of hospitalization among patients with T2DM. **Results.** Out of the total 549 COVID-19 positive patients treated, 124 (21.0%) had T2DM, while 470 (79.0%) did not have diabetes. Among patients with T2DM, men were significantly younger than women (60.6±16.8 vs. 64.2±15.3, p<0.01). The average hospitalization length in diabetic patients was 20.2±9.6 (from 5 to 54 days) and it was significantly longer (p than in non diabetic patients 15.0±3.4 ranged from 3 days up to 39 (t-test≈5.86, p<0.05). According to the results of the univariate regression analysis, each year of age is associated with an increase in the length of hospital stay by 0.06 days (95%CI: from 0.024 to 0.128, p=0.004). Patients who received oxygen therapy were treated for 2,8 days longer than those who did not receive oxygen treatment (95%CI: from 0.687 to 4,988, p=0.010), and each one-unit increase in CRP level was associated with a 0.02 day reduction in length of hospitalization (95%CI:from 0.004 to 0.029, p=0.008). Based on the results of the multivariate regression analysis, each year of age is associated with an increase in the length of hospitalization by 0.07 days (95%CI: from 0.022 to 0.110, p=0.003). Patients who received oxygen therapy were treated 3,2 days longer than those who did not receive oxygen therapy (95%CI: from 0.653 to 5,726, p=0.014), and each unit increase in CRP level was associated with a 0.02 day reduction in length of hospitalization (95%CI: from 0.005 to 0.028, p=0.004). Conclusion. Based on the presented results, diabetic COVID-positive patients had, on average, longer hospitalization than COVID non-diabetic patients. Hospital treatment of patients with with T2DM and with a milder form of COVID-19 was associated with older age, the use of oxygen therapy, and elevated CRP values. Patients who received oxygen therapy were treated approximately 3 days longer than those who did not receive this therapy. Understanding these factors is crucial for adjusting medical care and improving outcomes for these patients during the pandemic.

Keywords: type 2 diabetes mellitus; COVID-19; length of hospitalization

1. Background

The COVID-19 pandemic is a global health crisis that has placed a significant burden on healthcare systems worldwide [1]. Patients with diabetes mellitus (DM) are a particularly vulnerable population facing an increased risk of severe outcomes from COVID-19 infection, including prolonged hospitalization periods. DM as a chronic condition affecting the body's metabolic balance, can compromise the immune response and hinder the recovery process from infections [2].

In December 2019, cases of severe pneumonia with unknown etiology appeared in the human population in China [2]. The confirmation on January 7, 2020, was related to the identification of SARS-CoV-2 as the new causative agent of the corona virus disease 2019 (COVID-19). COVID-19 rapidly spread from China to the entire world and the World Health Organization (WHO) confirmed human-to-human transmission of the SARS-CoV-2 virus on January 23, 2020, and declared a pandemic on March 11, 2020 [3,4]. Based on data from the WHO, there have been cumulatively over 762 million confirmed cases of the infectious disease COVID-19 and more than 6.9 million deaths worldwide [5]. During the same period, according to the European Centre for Disease Prevention and Control in the EU/EEA territory, over 275 million confirmed cases of infection have been reported [6].

According to one meta-analysis estimated an overall pooled prevalence of 31% of DM in hospitalized COVID-19 patients [7] and with type 2 diabetes mellitus (T2DM). DM has been identified as the major comorbidity of hospitalized patients with COVID-19 [8–10]. The prevalence of DM in COVID-19 patients ranges from 5% to 36% [11,12]. Diabetics are a particularly vulnerable group of patients to infections [13], and during the COVID pandemic, it has been demonstrated that DM is a pro-inflammatory syndrome characterized by an inadequate cytokine response, with significantly higher concentrations of interleukin-6 (IL-6), ferritin, and C-reactive protein in the blood compared to non-diabetic COVID-positive patients [14–16]. It has been shown that uncontrolled glycemia in diabetic patients increases their vulnerability to inadequate immune response to infection further exacerbating the disease and leading to the development of acute respiratory distress syndrome (ARDS) and shock. The determined increased secretion of proinflammatory cytokines in diabetic patients may change the nature of the immune response to SARS-CoV-2 infection into inflammation, increasing the probability of a severe course of COVID-19, leading to a cytokine storm, tissue and respiratory damage [15,16]. Good glycaemic control may be important for maintaining the balance of the immune system [17].

Several studies have found associations between diabetes and greater odds of adverse clinical outcomes in COVID-19 including longer length of hospitalization, higher mortality rate, intensive care units (ICU) admission, and mechanical ventilation [18–20] and based on results of one retrospective analysis of 211,003 medical records, COVID-19 positive patients with T2DM had twice the risk of hospitalization [19]. Gottlieb et al. [20] and Martos-Benirez et al. [21] have reported similar results. In a large cross-sectional study in Mexico, COVID-positive patients with DM were 38.4% more likely to be hospitalized; and the estimated probability was higher if associated diseases were present. Halalau et al. [22] conducted a multicenter study to show a significant increase in the hospitalization of COVID-19 positive patients suffering not only from DM but also from pre diabetes.

Based on the finding from a study from the United States of America (USA) with almost a million participants, 20.5% of COVID-19 hospitalizations were attributable to DM; it is estimated that a 10% reduction in DM prevalence could reduce hospital admissions for COVID-19 infection by 2.7% [23]. Based on the results of a large study from the USA, DM was the second most frequent comorbidity, corresponding to 15% of COVID-19-infected individuals, while the prevalence of DM in the same region was 9.7% [24]. T2DM was also reported as an independent risk factor for ICU admission, after adjustment for age, sex, comorbidities, and insurance status [25]. Also, in a large cohort of COVID-19 hospitalized participants, patients with T2DM had higher rates of Intensive Intensive Coare Unit (ICU) admission and intubation, and longer hospital stay compared with non diabetic patients [26].

DM has not been proven that it is an independent factor in the hospitalization of COVID-19 positive patients [20]. The heterogeneity in the design of the aforementioned studies, and differences in local policy for COVID-19 spread prevention, may be responsible for the lack of consensus. In

addition to associated diseases, factors contributing to hospitalization diabetic patients included older age, male sex, delayed medical care and treatment [18–22].

The first confirmed case of the infectious disease COVID-19 in Serbia was registered on March 6, 2020, and the epidemic of greater epidemiological significance was declared on March 19, 2020. By the end of 2022, a total of 2,446,253 cases and 17,519 deaths were confirmed [27].

The main objective of this research was to explore factors associated with the length of hospitalization in diabetic patients with T2DM with mild form of COVID-19 in one tertiary university center in Serbia.

2. Material and Methods

2.1. Study Design

A retrospective cohort study in a single tertiary center was performed and it included all COVID-19 positive patients treated in the COVID department of the University Clinical Center (UCC) in Nis from 10 September 2021 to 31 December 2021. The total of number of COVID-19 patients with milder form of COVID-19 was 549 and they were not hospitalized in the intensive care unit (ICU) of the hospital's COVID-19 treatment. After obligatory testing for SARS-Cov2- polymerase chain reaction [PCR], the values of glycemia were checked by the Oral Glucose Tolerance Test (OGTT). Based on the results of this test and other medical documentation of the patients, all patients were divided into two groups: T2DM COVID-positive and only COVID-positive patients.

The study was done in accordance with Declaration from Helsinki. Decision of the University Clinical center (UCC) Ethics Committee Decision number 28827/2 dated 10/20/2020.

2.2. Data Sources and Patient Admission Procedure

Epidemiological, descriptive, clinical and laboratory data were taken from the electronic records of hospitalized patients with COVID-19. On admission to the COVID department, the medical history was taken and all patient characteristics, clinical symptoms of COVID-19 and the method of taking samples for COVID-19 testing were recorded. Also, on admission, patients with COVID-19 had their blood taken for biochemical analysis, and determination of blood count, kidney and liver function parameters: C-reactive protein, creatinine kinase, D-dimer, glycemia, HbA1c. The Oral Glucose Tolerance Test has done in some patients with specific symptoms such as: dry mouth, polydipsia, high blood glucose and medical documentation. All patients underwent radiography of the lungs. The patients were administered the specific COVID-19 therapy, oxygen therapy, and the vaccination status against COVID-19 was checked.

Table 1. Criteria of mild form of COVID-19 based on World Health Organization: COVID-19 disease severity [29].

Mild COVID-19 Illness
<ul style="list-style-type: none"> • Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia.
<ul style="list-style-type: none"> • Common symptoms include fever, cough, fatigue, anorexia, dyspnoea, and myalgia. Other non-specific symptoms include sore throat, nasal congestion, headache, diarrhoea, nausea/vomiting, and loss of smell/taste. Additional neurological manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke. Children may not report fever or cough as frequently as adults.
<ul style="list-style-type: none"> • Older people and immunosuppressed people may present with atypical symptoms (e.g., fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, absence of fever).
<ul style="list-style-type: none"> • Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g., dyspnoea, fever, gastrointestinal symptoms, fatigue) or other diseases (e.g., malaria) may overlap with COVID-19 symptoms.

2.3. Statistical Analysis

All collected data were entered into the electronic database and the software package SPSS version 22.0 was used for data processing. Univariate and multivariate regression analysis was used to determine the influence of certain factors on the length of hospitalization of patients with T2DM.

3. Results

Of the total number of treated COVID-positive patients, there were 124 (21.0%) with T2DM and 470 (79.0%) without diabetes. Men with T2DM were significantly younger than women (60.6 ± 16.8 vs 64.2 ± 15.3 , $p < 0.01$). Patients with T2DM had no significant differences in gender and age with non-diabetic patients ($p > 0.01$). There were significantly more vaccinated patients with T2DM against COVID-19, 70 (56.5%) than non-diabetic patients 142 (30.1%). The average hospitalization length in diabetic patients was 20.2 ± 9.6 (from 5 to 54 days) and it was significantly longer (p than in non-diabetic patients 15.0 ± 3.4 ranged from 3 days up to 39). Serum levels of CRP were much higher in diabetic patients and ranged from 2.2 to 325.0 and creatinine ranged from 45.0 to 771.4 than in those without diabetes (the CRP range from 1.0 to 224.0; the creatinine ranged from 42.0 up to 663.0). The diabetes group had a significantly higher average serum levels of CRP (than non-diabetic group ($p = 0.008$)). The diabetic patients had a significantly higher rate of preexisting comorbidities (65.0%, vs 48%) than non-diabetic patients.

Table 2 shows the results of univariate analysis of the most significant factors impacting the length of hospitalization of patients with T2DM and a mild form of COVID.

Table 2. Correlation between length of hospitalization and other investigated characteristics, the results of univariate and multivariate regression analyses.

Characteristics	R	95% CI limits		P
		Lower	Upper	
<i>Univariate regression analysis</i>				
Men	-1.004	-2.700	0.692	0.245
Age (years)	0.076	0.024	0.128	0.004
T2DM	1.189	-1.073	3.451	0.302
Vaccine	0.803	-0.916	2.522	0.359
Oxygen therapy	2.837	0.687	4.988	0.010
COVID-specific Th	0.180	-3.930	4.289	0.932
HbA1c	-1.864	-4.261	0.533	0.122
CRP	-0.017	-0.029	-0.004	0.008
Creatinine	-0.009	-0.019	0.002	0.100
DM duration	-0.244	-0.885	0.396	0.422
<i>Multivariate regression analysis</i>				
Men	-0.175	-1.572	1.222	0.805
Age (years)	0.066	0.022	0.110	0.003
T2DM	-0.952	-3.592	1.687	0.479
Vaccine	0.605	-0.920	2.130	0.436
Oxygen therapy	3.189	0.653	5.726	0.014
COVID-specific Th	-1.347	-5.078	2.383	0.478
HbA1c	-1.496	-3.011	0.020	0.053
CRP	-0.016	-0.028	-0.005	0.004
Creatinine	-0.008	-0.017	0.001	0.083
T2DM duration	-0.192	-0.759	0.375	0.507

According to the results of the univariate regression analysis, each year of age is associated with an increase in the length of hospitalization by 0.07 days (95%CI: from 0.024 to 0.128 days, $p = 0.004$). Patients who received oxygen therapy were treated for 2.8 days longer than those who did not receive

oxygen treatment (95%CI: from 0.687 to 4.988, $p=0.010$), and each one-unit increase in CRP level was associated with a 0.02 day reduction in length of hospitalization (95%CI: from 0.04 to 0.029, $p=0.008$).

Based on the results of the multivariate regression analysis, each year of age is associated with an increase in the length of hospitalization by 0.07 days (95%CI: from 0.022 to 0.110, $p=0.003$). Patients who received oxygen therapy were treated 3.2 days longer than those who did not (95%CI: from 0.653 to 5.726, $p=0.014$), and each unit increase in CRP level was associated with a 0.02 days reduction in length of hospitalization (95%CI: from 0.005 to 0.028, $p=0.004$).

Only 5% of the variability of hospitalization duration was determined by the characteristics examined in this research (coefficient of determination $R^2=0.050$).

4. Discussion

Based on the results of our study diabetic COVID-positive patients had, on average, longer hospitalization than COVID non-diabetic patients. The length of hospitalization of T2DM patients with mild COVID-19 was associated with older age, the use of oxygen therapy and elevated CRP values. Women with T2DM were significantly older than men.

Based on findings of Al-Salameh et al.'s diabetic patients with COVID-19 had a higher risk of death, ICU admission, and prolonged hospital stays [29]. Our results are in accordance with these results and with findings from the COVID hospitals from Serbia. According to the findings of the COVID hospital Batajnica from Serbia better metabolic control at admission was associated with shorter hospital duration and lower mortality rate in COVID positive diabetic patients, which implies the importance of prior glycemic control among patients with T2DM and CKD [30]. In the COVID hospital Zvezdara, out of 3664 patients, 960 (26.2%) had DM, which accounts for more than a quarter, and in over half of them, DM persisted for longer than 10 years [31].

There are also different findings available. According to Kusic et al., among the total number of examined COVID-positive patients, 68.6% had a comorbid condition, whereas 57.5% had a pre-existing cardiovascular disease (CVD). Statistical analysis confirmed that comorbidities did not significantly influence the duration of hospitalization. [32].

Our results indicated that age was one of the factors influencing longer hospitalization among diabetic COVID-positive patients. In our study women were significantly older than men and had longer hospitalization. Although the pathophysiological mechanisms are still not understood, it may be explained by the dysfunction of the immune system with aging. Age-specific rates per 100,000 inhabitants by gender during the year 2022 in the Republic of Serbia, due to the infectious disease COVID-19, were higher in all age categories among females, except in the age categories of 0–14 and 60 and above years, where a higher rate was observed among males. The highest age-specific rates of COVID-19 infectious disease incidence in the general population in Serbia were observed in the age group of 60 and above (13,556.91/100,000 inhabitants), while the lowest age-specific rate was recorded in the age group of 0–14 years at 6,525.68 per 100,000 inhabitants [28].

During the COVID-19 pandemic, there were significantly fewer hospitalized children and young people with type 1 diabetes mellitus (T1DM), which indirectly suggests that they were at lower risk of severe clinical presentation and that hospitalization was not necessary [7,11,12]. There hasn't been identified an increased risk of COVID-19 in children and in adults with T1DM [34] and there is also no documented evidence of increased mortality among these patients during the COVID-19 pandemic. According to previous studies, older diabetic patients were at higher risk for severe COVID-19 and eventually receive ICU admission and even death [12,21,22,35,36].

In a study conducted in China, it was determined that COVID-positive patients were mostly men (60%), but women more often had elevated body temperature and prolonged hospitalization. There were more women in the elderly population, so they were hospitalized more often, and the factor was older age with a high body temperature [33,34].

According to our results, one of the reasons for prolonged hospitalization was elevated CRP levels among diabetic patients. Similar data can be found in the literature. According to findings of Liu et al. increased CRP and lymphopenia are independent risk factors for COVID severity, while lymphopenia is also a risk factor for prolonged hospital stay [18].

In a study with COVID-positive patients with asymptomatic clinical picture and those with mild symptoms, conducted by Wu et al. it was determined that if diabetic patients had an elevated body temperature on admission, and it was the main reason for prolonged hospitalization [37]. The results of a retrospective study conducted in Vietnam showed that age, place of permanent residence and sources of infection were significantly associated with prolonged hospitalization of diabetic patients with T2DM and with COVID-19 during the second wave of COVID-19 pandemic [38].

Based on our findings diabetic patients who received oxygen therapy were treated approximately 3 days longer than those who did not receive this form of therapy. According to the results of a study conducted in Korea, DM was not an independent predictor of the severity of the clinical picture of the disease (which was defined as the need for oxygen therapy and/or artificial ventilation [39]. DM was a predictor of ICU admission, the occurrence of COVID-19 complications, and prolonged hospitalization duration [40,41]. A study in Western Sydney showed that patients with diabetes had 6% increase in mortality, 8% increase in ICU requirement, and 6.6 day increase in length of stay ($p < 0.01$) [42].

The control measures during the COVID-19 pandemic and the illness itself have impacted the deterioration of the health of patients with T2DM in several ways. Reduced mobility due to restrictions on outings in some countries due to lockdowns, irregular supply of dietary food and medications for diabetes, and associated conditions, as well as disruptions in regular medical check-ups and glycemic control. Many patients with symptoms of COVID-19 delayed seeking medical attention and testing due to fear of isolation, hospitalization, and separation from their families. There has been an increase in anxiety and depression among this group of patients and the entire population.

Limitations of the study. Laboratory biochemical tests were not performed for all patients nor was it possible to perform all important parameters. There is a lack of data on COVID-19 vaccination status for all hospitalized individuals. The interpretation of the results can also be affected by the sample size. In order to avoid mistakes, we took a sample of COVID-19 positive diabetic patients treated in the largest health care facility in the city of Nis and in the entire territory of the southeastern and southern Serbia.

Power of the study. The first study to determine factors that contributed to hospitalization and the length of hospitalization of diabetic patients with mild clinical form of COVID-19.

5. Conclusion

Based on the presented results, the length of hospital treatment of diabetic patients with a milder form of COVID-19 was associated with older age, the use of oxygen therapy, and elevated CRP values. Patients who received oxygen therapy were treated approximately 3 days longer than those who did not receive this therapy. Understanding these factors is crucial for adjusting medical care and improving outcomes for these patients during the pandemic.

Author Contributions: V.C.–Investigation, data curation, Writing – original draft ; N.R.- Conceptualization ; Formal analysis, Methodology, act as a corresponding author; M.P.- Conceptualization, Supervision, Validation; D.R. – Investigation, Data Curation , Resources, ; N.M. - Software, Investigation, Data Curation. All the authors approved the final version of the manuscript before submission.

Statement of Ethics: This study complied with the guidelines for human studies and included evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Study Approval Statement: This study was reviewed and approved by the Ethics Committee Decision of the UCC number 28827/2 dated 10/20/2020. Written informed consent was not obtained.

Data Availability Statement: The dataset underlying this study is available upon reasonable request from the first author or the corresponding author.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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