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Phenotypic characteristics and clinical outcome in hospitalized patients with COVID-19 and diabetes

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ABSTRACT

Objectives. The aim is to describe the phenotypic, biological and clinical characteristics of hospitalized patients with COVID-19 and diabetes, and the association with the clinical outcome of the patients.
Material and methods. This single-center, retrospective study was conducted on 200 patients. The primary endpoint was death observed within day 7, 14 and beyond day 14 of hospitalization, and secondary objective was to compare the survival group with non-survival group. The variables that demonstrated significant association with primary endpoint were subject to multivariate binary logistic regression analysis.
Outcomes. The estimated prevalence was 17.87% of the total COVID-19 hospitalizations during this period (n=1119). The majority of the patients were with diabetes mellitus type 2 with a median age of 67 years and BMI of 27.8 kg/m^2. On admission, 156 patients (78%) presented with severe/critical illness. A total of 93 patients (46.5%) met the primary endpoint, with most deaths occurring within day 7 of hospital stay. Non-survival group showed significantly higher levels of leucocytes count, more pronounced lymphopenia, higher CRP, LDH and D-dimer levels. Multivariate analysis identified four independent risk factors associated with death: age OR 1.05 (CI 95% 1.01-1.09), severity of disease at admission OR 0.22 (CI 95, 0.07-0.65), COVID-19 vaccination status OR 3.07 (CI 95%, 1.36-6.91) and LDH levels OR 1.00 (CI 95%,1.002-1.008).
Conclusions. Diabetic patients admitted to hospital for COVID-19 infection tend to have high mortality rate. Severity of disease at admission, advanced age, not completed vaccination and increased LDH levels are independent risk factors for lethal outcome, irrespective of diabetes status.

Keywords: COVID-19, diabetes, outcome, risk, severe

INTRODUCTION

More than two and a half years have passed since the declaration of COVID-19 pandemic on March 11th 2020 [1]. From then on, approximately half a billion cases emerged, amid concerns about testing and reporting issues in some countries [2]. With its broad clinical spectrum, COVID-19 manifests itself as a self-limiting respiratory tract infection [3,4]. However, some patients may rapidly develop serious complications, such as severe pneumonia with acute respiratory distress syndrome (ARDS), cardiorespiratory failure, shock, multiple organ failure and death [5]. People who are prone to develop severe disease are elderly patients or people of any age with underlying medical conditions, such as cardiovascular disease, diabetes mellitus, cancer, chronic lung and renal diseases [6]. Republic of North Macedonia, a land locked country in Western Balkans with population of around 2 million people, was severely affected by COVID-19 pandemic with fourth highest deaths per 1 million population in Europe [7].

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Diabetes mellitus (DM), a group of complex metabolic disorders, is a clinical syndrome associated with deficiency of insulin secretion or action [8]. It represents a major medical challenge of the 21st century with an estimated 463 million people living with diabetes mellitus in 2019, and the number is projected to increase by 25% in 2030 and 51% in 2045 [9]. Republic of North Macedonia has national estimated prevalence of 7.4% reported in IDF Diabetes Atlas from 2021 [10]. Besides the classical complications of the disease, diabetes mellitus is regarded as a critical risk factor for numerous infections. Characterized by hyperglycemic state with low-grade chronic inflammation and dysregulated innate immune response, patients have increased infection mortality and post-infection complications [11-13]. Furthermore, it was previously reported as major risk factor in 2009 H1N1 pandemic and Middle East respiratory syndrome coronavirus (MERS-CoV) [14,15]. In this context, it was quickly indicated that people with diabetes are at considerable risk for severe COVID-19 and are associated with poor outcome [16].

In this study, our primary objective is to describe the phenotypic traits of hospitalized patients with COVID-19 and diabetes mellitus and to identify the biological and clinical characteristics associated with the clinical outcome of the patients.

STUDY DESIGN AND METHODS

This single-center, retrospective, descriptive study was conducted in University Clinic for Infectious Diseases and Febrile Conditions, Skopje, between August 1st and December 31st 2021. Inclusion criteria were 1) hospitalized patients with COVID-19 diagnosis confirmed by SARS CoV-2 polymerase chain reaction (PCR) test; 2) radiologically verified pneumonia; 3) personal history of diabetes. Severity of the disease was defined using WHO (World Health Organization) COVID-19 disease classification [17]. The phenotypic description included age, sex, body mass index (BMI) and COVID-19 vaccination status. Diabetes and concomitant diabetic micro and macrovascular complications were self-reported by the patients or notified by the physician. The treatment for COVID-19 infection in all the hospitalized patients was according to the clinic adopted treatment protocol. Primary endpoint was death observed within day 7, 14 and beyond day 14 of hospitalization. The secondary objective was to compare the survival with non-survival group in terms of severity of disease at admission, COVID-19 vaccination status, other phenotypic and biochemical parameters. The patients' age, BMI and biochemical parameters were presented with a median value and interquartile range (IQR 25th- 75th percentile). Sex, micro and macrovascular complications, COVID-19 vaccination status, disease severity and outcome were given as number (percentage) of participants. Pearson's chi-squared test was applied to examine categorical data and Mann-Whitney test for continuous variables. The variables that demonstrated significant association with lethal outcome were subject to multivariate binary logistic regression analysis in order to identify independent predictors of outcome in patients with COVID-19 and diabetes. P values of <0.05 were considered statistically significant. All data analysis was performed on SPSS statistical software (version 25.0, SPSS Inc., Chicago, IL, USA).

The study was approved by the local ethics committee of the Medical Faculty in Skopje.

RESULTS

Between August 1st and December 31st 2021, 200 participants were included in the study with estimated prevalence of 17.87% of the total COVID-19 hospitalizations during this period (n=1119). The median age was 67, IQR 60-70 years, and gender distribution was 106 (53%) and 94 (47%) for man and woman, respectively. The Body Mass Index (BMI) was median 28.8 IQR 26.6-32 kg/m^2. Type 2 diabetes represented in the majority, concerning 197 (98.1%) of the patients. Micro and macrovascular complications from diabetes were presented in 66 (33%) and 68 (34%) of the individuals, respectively. The most common reported microvascular complications were diabetic retinopathy in 44 (66.66%) patients and diabetic nephropathy with 17 (25.75%) patients. Ischemic heart disease and cerebrovascular disease composing most of the macrovascular complications, presented in 27 (39.70%) and 21 (30.88%) patients, respectively. Of all patients, 77 (38.5%) had properly conducted COVID-19 vaccination prior hospital admission. On admission, 156 (78%) patients presented with severe to critical COVID-19 illness, and the rest, 44 (22%) patients, were with moderate clinical presentation. The phenotypic characteristics are shown in Table 1.

Biochemical analysis at admission, for the total participants, showed high C-reactive protein (CRP) levels, lymphopenia, increased lactate dehydrogenase (LDH) and D-dimer levels. The biochemical values are shown in Table 2.

A total of 93 patients (46.5%) did not survive. Overall, 65 (69.9%) deaths were reported within hospitalization day 7, 20 (21.5%) within day 14 and beyond hospitalization day 14 we noted 8 (8.6%) lethal outcomes. In contrast, only 15 patients (14.02%) were discharged by day 7, with most of hospital discharges occurred within day 14 in 67 (62.62%) patients.

TABLE 1. The phenotypic characteristics and COVID vaccination status in hospitalized patients with COVID-19 and diabetes

	Total (n=200, 100%)	Non-survivors (n=93, 46.5%)	Survivors (n=107, 53.5%)	p value*
Age, median (IQR), years	67 (60-72)	68 (62-74)	65 (57-71)	**0.018**
Sex				
Male	106 (53%)	49 (52.7%)	57 (53.78)	0.934
Female	94 (47%)	44 (47.3%)	50 (47.2%)	
Body mass index (BMI), median (IQR), kg/m^2	28.8 (26-32)	29.2 (26.7-32.8)	28.7 (26.4-32)	0.367
Microvascular diabetic complications	67 (33.5%)	37 (39.8%) †	30 (28.03%) †	0.079
Macrovascular diabetic complications	69 (34.5%)	38 (40.86%) †	31 (28.97%) †	0.078
Completed COVID vaccination	77 (38.5%)	24 (31.2%) †	53 (68.8%) †	**0.001**
Severity of disease at admission				
Moderate	44 (22%)	6 (13.6%)	38 (86.4%)	**<0.001**
Severe/Critical	156 (78%)	87 (55.8%)	69 (44.2%)	

**p values indicate differences between non-survival and survival group. A value of p<0.05 was considered statistically significant.*

†The percentages are calculated from the total participants.

TABLE 2. The biochemical values in hospitalised patients with COVID-19 and diabetes

	Total (n=193)	Non-survivors (n=93)	Survivors (n=107)	
	Median (IQR)	Median (IQR)	Median (IQR)	p value*
Hemoglobin	132 (120-142)	131(117-142)	133 (124-143)	0.153
Leucocytes	8.05 (5.7-11.2)	9.4 (5.8-12.6)	7.9 (5.6-10)	**0.044**
Lymphocytes	11 (7-11)	9 (6-15)	12 (8-17)	**0.007**
Thrombocytes	223 (162-284)	223 (153-284)	227 (170-299)	0.406
Urea nitrogen	7.3 (4.6-10.8)	9 (6.4-14)	5.4 (3.8-8.5)	**<0.001**
Creatinine	83 (63-113)	98 (76-151)	71 (56-89)	**<0.001**
Glucose	11.9 (9-17.7)	12.6 (9.2-21.6)	11.7 (8.9-15.6)	0.165
Alanine aminotransferase (ALT)	34 (20-50)	26 (21-48)	35 (20-52)	0.367
Aspartate aminotransferase (AST)	46 (32-69)	52 (34-76)	43 (31-65)	**0.034**
Creatinine kinase (CK)	115 (54-250)	156 (63-349)	90 (49-177)	**0.015**
Lactate dehydrogenase (LDH)	419 (324-561)	522 (407-645)	359 (300-446)	**<0.001**
C-reactive protein (CRP)	107 (70-174)	128 (79-191)	94 (57-153)	**0.006**
D-dimer	760 (478-1884)	1216 (571-2561)	653 (373-1199)	**<0.001**

**p values indicate differences between primary outcome and survival group. A value of p<0.05 was considered statistically significant*

Analyzing above mentioned variables with consideration of the primary outcome, significant correlation was noted with severity of disease at admission (p<0.001), vaccination status (p<0.001), and age (p= 0.018), i.e., non-survivors tend to be older, and more likely to have severe to critical disease at admission and without completed COVID-19 vaccination. The rate of microvascular and macrovascular complications showed no statistical significance between the two groups, but showed a higher trend in patients who deceased. Deceased patient group, in comparison with the survival group, showed significantly higher levels of leucocytes count (p=0.044), urea nitrogen and creatinine levels (both p<0.001), more pronounced lymphopenia (p=0.007), higher C-reactive protein (p=0.006), aspartate aminotransferase (p=0.034), lactate dehydrogenase (p<0.001) and D-dimer levels (p<0.001).

Multivariate binary logistic regression analysis determined four factors independently associated with the risk of death: age, severity of disease at admission, COVID-19 vaccination status and increased lactate dehydrogenase levels. The results of the multivariable analysis are shown in Table 3.

TABLE 3. Multivariate binary logistic regression analysis with death as the dependent factor

Factors	OR * (95% CI *)	p value
Age	1.052 (1.012-1.094)	0.011
Severity of disease at admission	0.222 (0.075-0.659)	0.007
Not completed COVID vaccination	3.075 (1.367-6.918)	0.007
Lactate dehydrogenase (LDH) level	1.005 (1.002-1.008)	0.001

* *OR, Odds ratio; CI, confidence interval*

DISCUSSION

This is the first study dedicated to inpatients with COVID-19 and diabetes mellitus in Republic of North Macedonia, carried out at University Clinic for Infectious Diseases and Febrile Conditions, Skopje. The prevalence of diabetes in inpatient COVID-19 ranged from 5-20% in Chinese studies [18-20], 12.1% in Greece [21] to 28.3% in USA reported in COVID-19 - Associated Hospitalization Surveillance Network (COVID-NET) [22]. The prevalence in our study is in accordance with other observations with high diabetes mellitus prevalence among hospitalized COVID-19 patients. Diabetes prevalence is two- to threefold higher in patients in intensive care unit (ICU) reported in Lombardy, Italy [23] and New York, USA [24] with increased mortality compared with patients without diabetes mellitus.

The mortality rate in our study was high. A study from Greece reported 32.5% in-hospital case fatality rate among 157 diabetic COVID-19 patients [21]. Similarly, a report from England nationwide register-based study found an in–hospital COVID –19 fatality rate of 31.4% in diabetic patients [25]. The CORONDO study from France reported 29.0% fatality rate from 1317 patients with COVID-19 and diabetes [26].

Aging is positively correlated with obesity, infection mortality, concomitant diabetic complications and other geriatric conditions [27]. A higher proportion of elderly patients falls within the non-survival group, and we presented that age is an independent risk factor for lethal outcome, which is in line with other studies [28-30]. Our study participants' body mass index falls within obesity range. Obesity is constantly reported as risk factor for COVID- 19 hospital admission, requirement for mechanical ventilation and death, irrespective of diabetic status [31,32]. Non-survival group showed a slightly higher trend in BMI, but statistical significance was not found.

Poor glycemic control and chronic hyperglycemia consequently causing endothelial dysfunction is the cornerstone for developing microvascular and macrovascular complications in patients with diabetes mellitus [35,36]. Several studies associate both endothelial dysfunction in diabetes and in COVID-19, hypothesizing as the pathophysiological mechanisms behind increased COVID-19 severity and mortality in diabetic patients [37]. In our study, microvascular and macrovascular complications were slightly lower than in The CORONDO study from France which reported 44.2 and 38.6% for micro and macrovascular complications, respectively, present in hospitalized patients with COVID-19 and diabetes [27,38]. They also identified underlying microvascular retinopathy and diabetic kidney disease as risk factor for death observed withing day 7 of hospitalization [27,38]. Another single center study of 187 hospitalized COVID-19 patients with diabetes reported diabetic retinopathy as independent risk factor for ICU admission and mechanical intubation [39]. Leon-Abarca et al. reported that patients with diabetic nephropathy have an increased probability of adverse outcomes in COVID-19 disease [40]. Diabetic retinopathy and diabetic nephropathy were the most commonly reported microvascular complications in our study.

With the development of the COVID-19 vaccines, it was initially prioritized for patients with increased risk for severe COVID-19, including diabetic patients, with dozens of studies concluded their efficacy and effectiveness. Not completing covid vaccination schedule represent independent factor for the clinical outcome in COVID-19 patients [33,34], which is in accordance with our observation.

The evident biochemical abnormalities in our study go in line and reflect the severity of the disease. These observations suggest that the COVID-19 and diabetes inpatients were at higher risk for developing cytokine storm or accompany bacterial infection. Yan Y et al reported from study conducted on 193 hospitalized patients, of whom 24,8% had diabetes, that diabetic patients had elevated levels of leucocytes count, C-reactive protein, D-dimer and lactate dehydrogenase levels, results which are comparable with our study [41]. The CORONDO nationwide study from France on inpatients with COVID-19 and diabetes mellitus, reported several biological parameters reflecting the severity of the disease and were also associated with lethal outcome, such as C-reactive protein, lymphopenia, creatinine kinase, AST levels and reduced kidney function [37]. These findings were in line with our results.

The limitations in our study are discussed as follows.

First, this is a retrospective single-center study, and more prospective studies conducted at more large-scale multicenter studies are needed.

Second, the study was conducted at University Clinic for Infectious Diseases and Febrile Condi-

tions- Skopje, a single tertiary care center for infectious diseases in Republic of North Macedonia. This public health institution generally admitted patients with severe to critical illness, many of whom had already advanced illness, with 78% of the participants having severe to critical illness. The real mortality in patients with severe COVID-19 and diabetes still needs further study on a larger scale.

Third, the study results are in comparison with others studies conducted in more developed countries, who have consequently superior healthcare systems, with better initial COVID-19 treatment and vaccination coverage, lower diabetes mellitus prevalence, better diabetes mellitus management and glycemic control prior infection. No other similar studies from other neighboring developing countries were found.

In summary, our findings demonstrated that diabetic patients admitted to hospital for COVID-19 infection tend to be obese senior patients with severe to critical disease at admission and with high mortality rate. Elderly patients without completed COVID-19 vaccination and high levels of lactate dehydrogenase are particularly at risk of death from COVID-19 irrespective of diabetic status.

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