UDC 616.981.21/.958.7+612.112.71

Hematological features of patients with type 2 diabetes depending on the variant of SARS-COV-2

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The aim of our work was to investigate the peculiarities of hematological indicators in patients with COVID-19 depending on the variant of SARS-CoV-2. A retrospective study of the electronic medical records of 19 patients with the delta variant (7 patients had comorbidity with type 2 diabetes (T2D); 12 patients without T2D - control group) and 46 patients with the omicron variant (26 patients had comorbidity with T2D; 20 patients without T2D - control group). No statistically significant differences were found in gender, the number of leukocytes, lymphocytes, and granulocytes in peripheral blood, C-reactive protein, and D-dimer. The results also showed a significant difference in procalcitonin level and monocyte count in patients with delta variant and T2D. A predictive model was developed using binary logistic regression to determine the SARS-CoV-2 variant based on hematological parameters (sensitivity - 76.5%, specificity - 84.8%). Thus, the peculiarities of hematological indicators of patients with T2D depending on the variant of SARS-CoV-2 (delta or omicron) were established.
Key words: coronavirus infection; type 2 diabetes; omicron; delta; procalcitonin.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 [1, 2]. The severity of COVID-19 ranges from asymptomatic to severe infection leading to death [1]. Since December 2019, three waves of infections linked to the advent of SARS-CoV-2 have occurred, dubbed the alpha, beta, and delta variants [3, 4]. In November 2021, a new SARS-CoV-2 variant of concern - B.1.1.529 (omicron) - was reported in South Africa [5]. The omicron variant of SARS-CoV-2 has demonstrated high transmissibility, with early studies indicating lower severity of infection than that of the delta variant (B.1.617.2) [6-8].

Studies report that, depending on different areas, 20–50% of COVID-19 patients suffer diabetes [9], and they have shown increased risk of COVID-19 developing if compare with nondiabetic patients [10-12]. Diabetes is a chronic disease that affects over 463 million people around the world [13]. Type 2 diabetes mellitus (T2D) is equally common in patients with delta and omicron strains [14], but the possible occurrence of alternative ways of virus entry in people affected by diabetes, as recently suggested [15], makes the new omicron virus mutation of particular interest in patients with diabetes. Whether this new variant may influence the real-world clinical evolution of COVID-19 in people affected by diabetes mellitus is still a matter of speculation [16].

Our work aimed to establish the laboratory characteristics of patients with T2D and COVID-19 in periods of omicron and delta variants predominance.

METHODS

This was a retrospective study conducted at the Transcarpathian Regional Clinical Infectious Diseases Hospital (Uzhhorod, Ukraine). We used data collected from patients' medical

records available from e-health information system, which included all adult patients (≥18 years old) admitted from January 2021 to March 2022 with SARS-CoV-2 diagnosis confirmed by Polymerase Chain Reaction (PCR) analysis of a nasal swab. The study included 19 patients with delta, of whom 7 patients had T2D, and 46 patients with omicron, of whom 26 had TD2M. A study flow diagram is shown in Fig. 1.

Demographics, comorbidities, laboratory tests, and treatments of COVID-19 patients with and without T2D were collected from electronic medical records (EMR)

Results were expressed as mean ± standard deviation (SD). The classification variable was represented as a count (%). Differences in parameters between groups were analysed using the Student's t-test for variables with a normal distribution. The Mann–Whitney U-test was employed for continuous variables with a non-normal distribution, and the χ^2 test was used for categorical variables. All statistical analyses were performed using SPSS software. $P \leq 0.05$ was considered to indicate statistical significance. Using binary logistic regression, a prognostic model was developed to determine the SARS-CoV-2 variant based on hematological parameters.

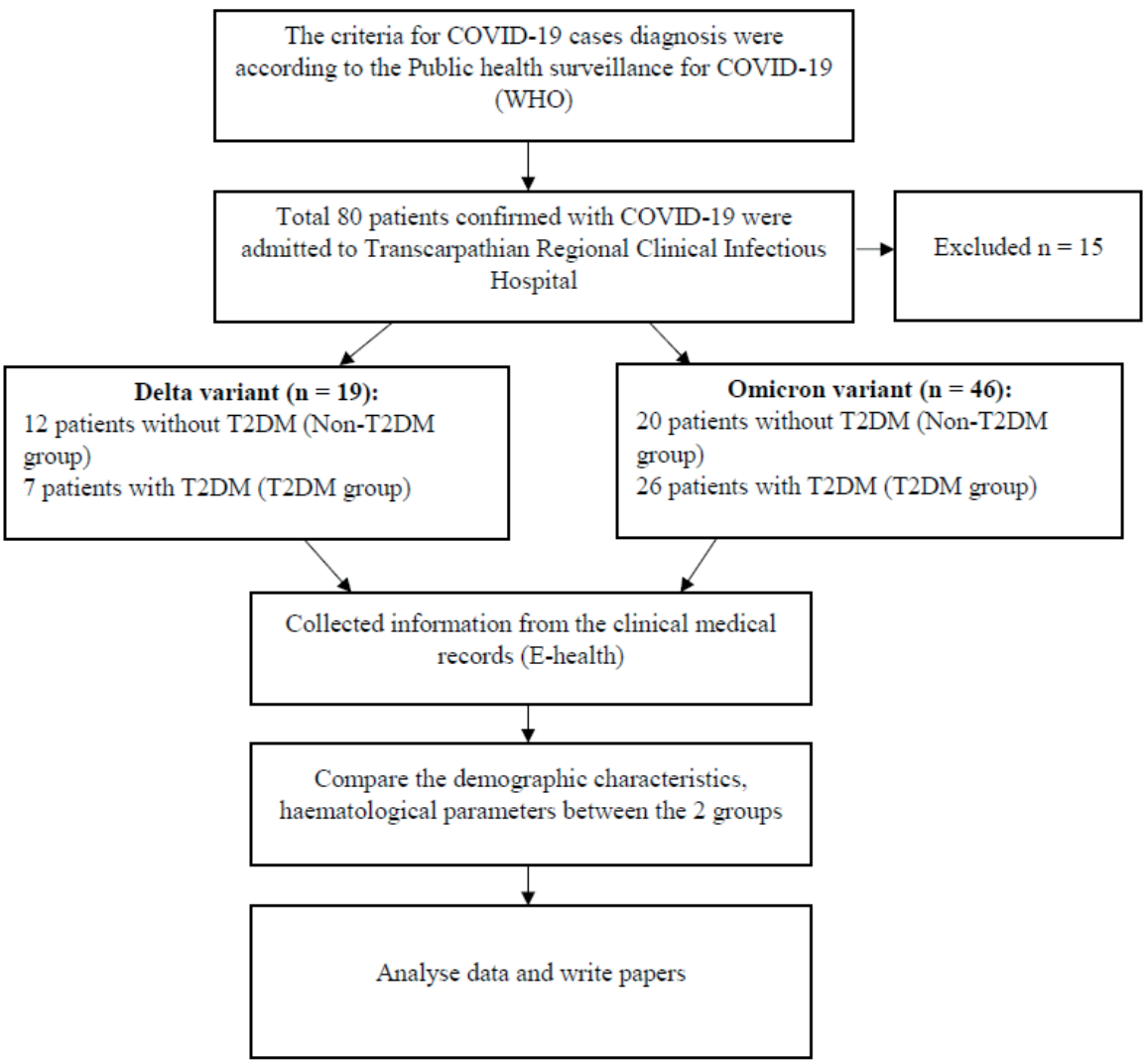

Fig. 1. Study flow diagram

RESULTS

Our study included 65 hospitalized patients with COVID-19. As shown in Table 1, 33 (50.7 %) patients with T2D and 32 (49.3 %) patients without diabetes were enrolled. Compared with nondiabetic patients, patients with diabetes were older in groups with delta and omicron variants.

There were no significant differences in creatinine (P = 0.692), granulocytes count (P = 0.227), serum C reactive protein (CRP) (P = 0.462), D-dimer (P = 0.926) and levels of procalcitonin (P = 0.843). Interestingly, the absolute number for white blood cell counts and lymphocytes was higher in the T2D group compared to the Non-T2D group (White blood cells (WBCs), 9.28 ± 4.46 vs 6.36 ± 2.80, P = 0.096; lymphocytes, 1.32 ± 0.47 vs 0.86 ± 0.30). These two groups showed no significant differences in creatinine (P = 0.706), granulocytes count (P = 0.101), CRP (P = 0.758), D-dimer (P = 0.605), levels of procalcitonin (P = 0.331), WBC (P= 0.223) and lymphocyte counts (P = 0.258). The average procalcitonin levels (P = 0.003) and monocyte counts (P = 0.001) in T2D patients with delta variant of SARS-CoV-2 infection showed a significant difference if compare with the omicron variant. As shown in Table 2, compared with the non-T2D patients, patients with diabetes were more likely to have cardiovascular disease.

Patients with COVID-19 and TD2 who took insulin had higher levels of granulocytes than patients who didn`t take insulin (P = 0.022, respectively). When comparing of WBCs, lymphocytes, CRP, D-dimer, creatinine, procalcitonin depending on insulin treatment there were no statistically significant differences (P = 0.082, P = 0.430, P = 0.846, P = 0.181, P = 0.647, P = 0.340, respectively).

As shown in Fig. 2, patients taking metformin had significantly lower CRP levels (P = 0.046). When comparing of WBC, granulocytes, lymphocytes, D-dimer, creatinine, procalcitonin

Table 1. Demographic and laboratory findings of patients with and without T2D infected with COVID-19 (delta and omicron variants)

Variables	Delta variant (DV)		P	Omicron variant (OV)		P	DV with T2D vs OV with T2D P
	Non-T2D n = 12	T2D n = 7		Non-T2D n = 20	T2D n = 26		
Age (Mean ± SD)	53.66 ± 13.37	67.00 ± 7.70	0.022*	55.75 ± 15.02	70.42 ± 8.86	0.000*	0.360
Gender (M/F)	6/6	3/4	-	1/19	8/18	-	-
Creatinine (μmol/l)	107.94 ± 17.73	112.74 ± 34.62	0.692	104.23 ± 19.63	121.00 ± 82.10	0.706	0.798
Leukocytes (WBC) ($\times 10^9$/l)	6.36 ± 2.80	9.28 ± 4.46	0.096*	9.48 ± 4.99	10.67 ± 3.76	0.223	0.406
GRA ($\times 10^9$/l)	5.49 ± 2.79	7.98 ± 4.40	0.227	7.83 ± 5.03	9.24 ± 3.69	0.101	0.449
LY ($\times 10^9$/l)	0.86 ± 0.30	1.32 ± 0.47	0.028*	1.32 ± 0.52	1.18 ± 0.55	0.258	0.528
MON ($\times 10^9$/l)	0.07 ± 0.003	0.001 ± 0.002	0.001*	0.1 ± 0.02	0.3 ± 0.20	0.325	0.001*
CRP (mg/l)	88.45 ± 62.06	67.14 ± 34.11	0.462	69.62 ± 70.36	71.70 ± 14.06	0.758	0.751
D-dimer (mg/l)	0.88 ± 0.55	0.90 ± 0.64	0.926	3.18 ± 4.04	2.63 ± 3.10	0.605	0.157
Procalcitonin (ng/ml)	0.05 ± 0.02	1.45 ± 0.91	0.843	0.71 ± 0.69	0.06 ± 0.02	0.331	0.003*

* association of the outcome value with the predictor value is statistically significant (P < 0.05)

Table 2. Characteristics of patients with and without T2D infected with COVID-19 (delta and omicron variants)

Variables	Delta variant (DV)		Omicron variant (OV)	
	Non-T2D	T2D	Non-T2D	T2D
Comorbidities at admission:				
Cardiovascular and cerebrovascular, n (%)	3 (25 %)	7 (100 %)	12 (60 %)	23 (88.4 %)
Malignant tumors, n (%)	0	0	0	1 (3.8 %)
Digestive system disease, n (%)	0	0	1 (5 %)	0
Respiratory system diseases, n (%)	2 (16.6 %)	0	0	1 (3.8 %)
Nervous system diseases, n (%)	0	0	1 (5 %)	1 (3.8 %)
Medicine control for diabetes:				
Insulin, n (%)	0	6 (85.7 %)	0	19 (73.0 %)
Metformin, n (%)	0	4 (57.1 %)	0	8 (30.7 %)

depending on metformin treatment, there were no statistically significant differences (P = 0.463, P = 0.315, P = 0.666, P = 0.544, P = 0.644, P = 0.660, respectively).

Also, to determine the variant of SARS-CoV-2 based on hematological parameters (Fig. 3; Table 3), the following mathematical model was developed:

$P = 1 / (1 + e^{-z}) \times 100\%$, where P – probability of delta variant, and $z = 1.506 - 0.102 \times$ glucose $+ 0.104 \times$ WBC $- 0.269 \times$ granulocytes $+ 0.754 \times$ lymphocytes $- 6.695 \times$ monocytes $+ 0.562 \times$ procalcitonin $- 0.002 \times$ CRP.

The resulting regression model is statistically significant ($P < 0.001$). Based on the value of Nagelkerke R^2, the model explains 41.6% of the observed Variants variance. For each unit increase in monocytes, delta-variant odds associate with 808.031 times decrease (Fig. 3).

The area under the ROC curve comprised 0.845 ± 0.047 with 95% CI: 0.754 - 0.937. The resulting model was statistically significant ($P < 0.001$) (Fig. 4). The cut-off value of logistic function P is 0.560, this corresponds to the highest Youden's J statistic. If logistic function P is greater than or equal to this value, the delta variant will be predicted. The sensitivity and specificity of the method are 76.5% and 84.8%, respectively (Fig. 5).

DISCUSSION

The first omicron case was recorded on 9 November 2021 in the city of Tshwane. This led

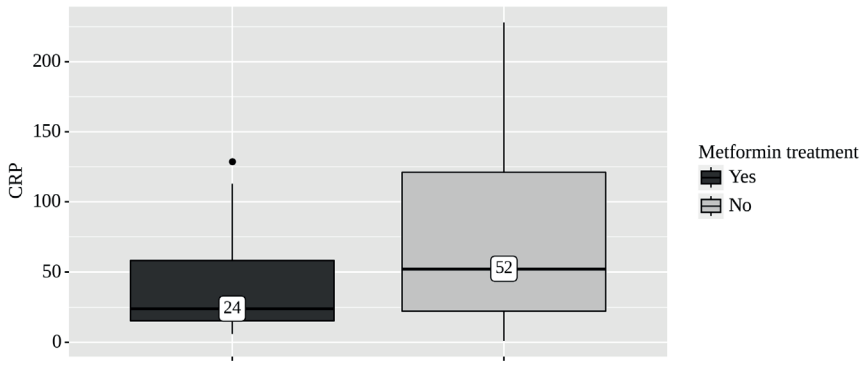

Fig. 2. CRP levels in patients with TD2 and COVID-19 depending on metformin treatment

Table 3. Characteristics of the association of predictors with the probability of the variant (delta or omicron)

Predictors	Unadjusted		Adjusted	
	COR; 95% CI	P	AOR; 95% CI	P
Glucose	0.890; 0.804 – 0.986	0.025*	0.903; 0.801 – 1.018	0.094
Leukocytes (WBC)	0.836; 0.733 – 0.953	0.007*	1.109; 0.279 – 4.415	0.883
Granulocytes	0.821; 0.714 – 0.944	0.006*	0.764; 0.192 – 3.050	0.703
Lymphocytes	0.917; 0.444 – 1.896	0.816	2.126; 0.348 – 12.975	0.414
Monocytes	0.008; 0.000 – 0.165	0.002*	0.001; 0.000 – 0.071	0.001*
Procalcitonin	0.892; 0.496 – 1.605	0.703	1.755; 0.717 – 4.293	0.218
CRP	0.995; 0.987 – 1.003	0.194	0.998; 0.988 – 1.007	0.647

* association of the outcome value with the predictor value is statistically significant ($P < 0.05$)

to a rapid increase in SARS-CoV-2 infections and hospitalizations associated with COVID-19 since 14 November 2021, marking the beginning of the fourth wave in South Africa. The omicron variant rapidly displaced delta in the City of Tshwane and the Gauteng Province of South Africa [17]. The Technical Advisory Group on the Evolution of SARS-CoV-2 Virus (TAG-VE) has informed WHO that the Omicron variant should be designated as an important variant (VOC), due to the epidemiological parameters initially reported in South Africa, and now spreading around the world [18]. Using Artificial Intelligence modelling, it was calculated that the omicron variant is 10× and 2× as contagious as the original SARS-CoV-2 variant and the delta variant, respectively. This increase in infectivity is considered due to the mutations [19]. Initial reports suggest that the omicron variant is more transmissible and resistant to vaccine neutralization but causes less severe illness compared with previous variants [20].

Diabetes has emerged as an important risk factor for severe illness and death from COVID-19 [10]. The worse outcome of COVID-19 in people with diabetes mellitus could be related to the non-enzymatic glycation of human ACE2, leading to a more susceptible interaction with virus spike protein [15]. The computational analysis results allow us to hypothesize that affinity between the viral protein Spike and the human receptor ACE2 is

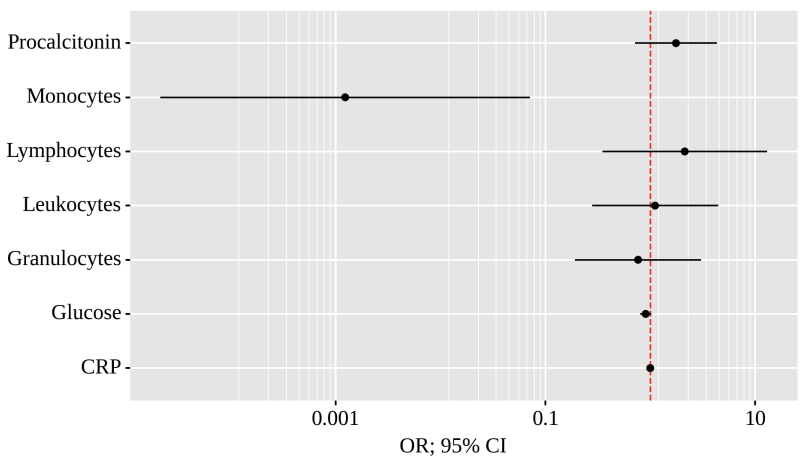

Fig. 3. Odds ratios estimates with corresponding 95% CI's for predictors included to the model

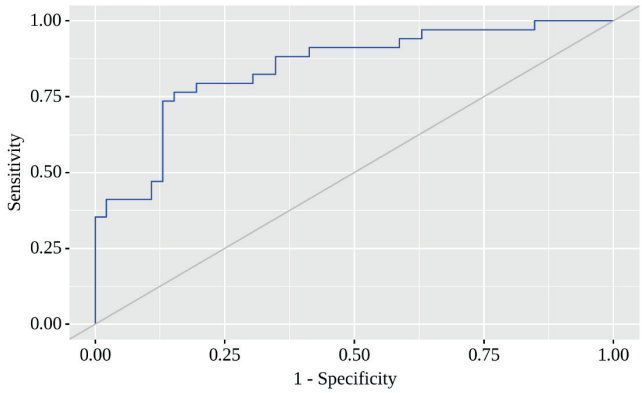

Fig. 4. ROC-curve characterizing the dependence probability of the variants (delta or omicron) on the value of logistic function P

higher for the omicron variant concerning the wild-type SARS-CoV-2 both in native conditions and also in the case of non-enzymatic glycation, typical of the hyperglycaemic environment [16].

According to a study by Zhenkui Hu et al. [21]. T2D occurs at the same frequency in both the Delta and wild variants of SARS-CoV-2 infection. Patients with T2D who had omicron variant were characterized by lower levels of procalcitonin than patients with delta variant, which may indicate a more severe inflammatory reaction. Our study showed that the course of delta and omicron variants of SARS-CoV-2 infection in patients with T2D did not differ from the main laboratory parameters (excluding procalcitonin), this indicates that to some extent our study confirms the study by Modes et al. [20].

Metformin is now considered the first-line T2D treatment agent [22]. Historically, because of its host-directed antiviral properties, metformin was used during the treatment of influenza outbreak [23]. Based on the pathogenesis of SARS-CoV-2, several mechanisms have been proposed on the possible beneficial effects of metformin on COVID-19 patients with pre-existing T2D, such as anti-inflammatory effects, increasing the cellular pH to inhibit viral infection [24]. It has been confirmed in many studies that metformin has anti-inflammatory properties, reduces CRP, and increases the survival rate of COVID-19 patients [25, 26].

As for patients with diabetes who took insulin, studies have shown an increased risk of death in confirmed COVID-19 cases [27, 28]. A model study in diabetic mice showed that the

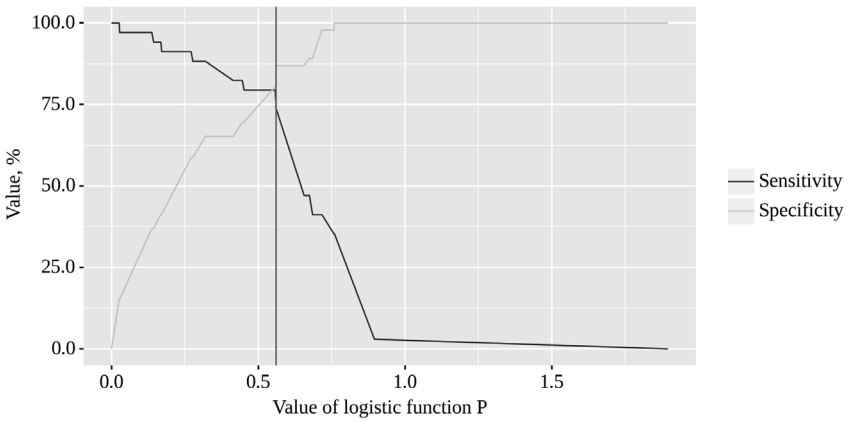

Fig. 5. Analysis of the sensitivity and specificity of prognosis variants (delta or omicron) depending on logistic function P

expression of ACE2 increased during insulin therapy, which could lead to an aggravated result in patients with COVID-19 [29, 30].

CONCLUSIONS

The peculiarities of hematological indicators of patients with type 2 diabetes depending on the variant of SARS-CoV-2 (delta or omicron) were established. Using binary logistic regression, a predictive mathematical model was developed to determine the SARS-CoV-2 variant (sensitivity – 76.5%, specificity – 84.8%).

We would like to thank all the patients who participated in our study. Also, we thank the director of the Transcarpathian Regional Clinical Infectious Diseases Hospital, Mykhailo Polyak, for his assistance in conducting this study.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ОСОБЛИВОСТІ ГЕМАТОЛОГІЧНИХ ПОКАЗНИКІВ ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ ЗАЛЕЖНО ВІД ВАРІАНТУ SARS-COV-2

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Метою нашої роботи було дослідити особливості гематологічних показників у пацієнтів із COVID-19 в залежності від варіанту SARS-CoV-2. Проведено ретроспективне дослідження електронних медичних карток 19 пацієнтів з дельта-варіантом (7 пацієнтів мали коморбідність із цукровим діабетом 2-го типу (ЦД2); 12 пацієнтів без ЦД2 – контрольна група) та 46 пацієнтів з варіантом омікрон (26 пацієнтів мали коморбідність із ЦД2; 20 пацієнтів без ЦД2 – контрольна група). Не виявлено статистично значущих гендерних відмінностей, а також за кількістю лейкоцитів, лімфоцитів та гранулоцитів у периферичній крові, вмістом С-реактивного протеїну та D-димера. Слід відмітити збільшення вмісту прокальцитоніну та кількості моноцитів у периферичній крові у пацієнтів з дельта варіантом та ЦД2 порівняно з варіантом омікрон. За допомогою бінарної логістичної регресії було розроблено прогностичну модель для визначення варіанту SARS-CoV-2 на основі гематологічних параметрів (чутливість – 76.5%, специфічність – 84.8%). Таким чином, встановлено особливості гематологічних показників пацієнтів з цукровим діабетом 2-го типу залежно від варіанту SARS-CoV-2 (дельта чи омікрон).

Ключові слова: коронавірусна інфекція; цукровий діабет 2-го типу; омікрон; дельта; С-реактивний білок; прокальцитонін; Д-димер.

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Received 31.10.2022