THE IMPACT OF CARBOHYDRATE METABOLISM DISORDERS ON THE EARLY AND LONG-TERM CLINICAL OUTCOMES OF PATIENTS WITH COVID-19 ACCORDING TO THE ACTIV AND ACTIV 2 REGISTRIES

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BACKGROUND: Numerous studies indicate a high incidence of various disorders of carbohydrate metabolism against the new coronavirus infection. These disorders aggravate the course of infection and increase mortality. Thereby, analysis of risk factors for unfavorable outcomes and assessment of the long-term consequences of COVID-19 in patients with impaired carbohydrate metabolism is of great importance.
AIM: To investigate the association between carbohydrate metabolism disorders in COVID-19 patients and mortality, course of infection, long-term consequences, as well as to identify risk factors for an unfavorable disease course.
MATERIALS AND METHODS: A retrospective analysis of data from the combined multicenter non-interventional real-world AKTIV and AKTIV 2 registries was performed. The sample included 9290 patients who had COVID-19 with varying severity from June 29, 2020, to November 29, 2020 (ACTIV) and from October 01, 2020, to March 30, 2021 (ACTIV 2). The patients were divided into 3 groups: Group 1 — patients with intact carbohydrate metabolism, n=6606; Group 2 — patients with newly diagnosed hyperglycemia (NDH), n=1073; Group 3 — patients with a history of type 2 diabetes mellitus (DM2), n=1611. The groups were assessed for clinical and laboratory parameters, comorbidities, mortality, carbohydrate metabolic status, and well-being during the infection and at 12 months.
RESULTS: The prevalence of carbohydrate metabolism disorders (CMD) was 28,9%, with DM2 patients accounting for 17,3% and patients with newly diagnosed hyperglycemia (NDH) for 11,6%. The mortality rate of patients with hyperglycemia of any origin was 10.6%, which was significantly higher compared to patients without hyperglycemia (3,9%). The probability of lethal outcome increased 2,48-fold in the group of patients with DM2 and 2,04-fold in the group of patients with NDH. At the same time, the probability of a lethal outcome decreased 2,94-fold in patients without CMD. At 12 months, patients with CMD showed a significantly higher frequency and longer persistence of complaints. This trend was more pronounced in patients with DM2 than in those with NDH. Only 1,7% of patients from the NDH group had type 2 diabetes and were receiving oral hypoglycemic medications one year after the infection. A prognostic model was developed to determine the risk of lethal outcome. The model included such known predictors as concomitant ischemic heart disease, history of myocardial infarction or stroke, blood glucose level, and age.
CONCLUSION: Carbohydrate metabolism disorders aggravate the course of COVID-19 and increase mortality. One year after infection, patients with DM2 and NDH were more likely to have symptoms typical for post-COVID syndrome, and NDH resolved in most cases after the infection.

KEYWORDS: COVID-19; type 2 diabetes mellitus; hyperglycemia; mortality; predictors.

ВЛИЯНИЕ НАРУШЕНИЙ УГЛЕВОДНОГО ОБМЕНА НА РАННИЕ И ОТДАЛЕННЫЕ КЛИНИЧЕСКИЕ ИСХОДЫ У ПАЦИЕНТОВ С COVID-19 ПО ДАННЫМ РЕГИСТРОВ АКТИВ И АКТИВ 2

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ОБОСНОВАНИЕ. Многочисленные исследования свидетельствуют о высокой встречаемости различных нарушений углеводного обмена (НУО) при новой коронавирусной инфекции (НКИ), утяжеляющих ее течение и приводящих к большей частоте смертельных исходов. Это актуализирует поиск факторов риска неблагоприятных исходов и оценку отдаленных последствий COVID-19 у пациентов с НУО.
ЦЕЛЬ. Изучить взаимосвязь НУО у пациентов с COVID-19 с летальностью, течением инфекции и отдаленными последствиями, а также выявить факторы риска неблагоприятного течения заболевания.
МАТЕРИАЛЫ И МЕТОДЫ. Выполнен ретроспективный анализ данных объединенных многоцентровых неинтервенционных регистров реальной клинической практики АКТИВ и АКТИВ 2, включивший 9290 пациентов с COVID-19 различной степени тяжести, перенесенной в период с 29.06.2020 г. по 29.11.2020 г (АКТИВ) и с 01.10.2020 г. по 30.03.2021 г. (АКТИВ 2). Пациентов разделяли на группы: группа 1 — пациенты без НУО, n=6606, группа 2 — пациенты с впервые выявленной гипергликемией (ВВГ), n=1073, группа 3 — лица с сахарным диабетом 2 типа (СД2) в анамнезе, n=1611. В группах оценивали клинико-лабораторные показатели, наличие сопутствующей патологии и летальность в период инфекции, а также через 12 мес — состояние углеводного обмена пациентов и их самочувствие.
РЕЗУЛЬТАТЫ. Распространенность НУО составила 28,9% случаев, из которых 17,3% — СД2, а 11,6% случаев представлены ВВГ. Летальность пациентов с гипергликемией любого генеза составила 10,6% случаев, что значимо выше по сравнению с пациентами без таковой (3,9%), шансы наступления летального исхода у больных с СД2 увеличивались в 2,48 раза, а в группе пациентов с ВВГ — в 2,04 раза, у пациентов без НУО летальность, напротив, уменьшалась в 2,94 раза. Через 12 мес у пациентов с НУО выявлено значимо большее количество жалоб с преобладанием их у пациентов с СД2. Спустя год после инфекции в группе лиц с ВВГ только 1,7% имели СД2 и получали пероральные сахароснижающие препараты. Разработанная прогностическая модель определения риска развития летального исхода основывается на выявленных предикторах: сопутствующая ишемическая болезнь сердца, инфаркт миокарда или инсульт в анамнезе, более высокая гликемия и старший возраст.
ЗАКЛЮЧЕНИЕ. НУО приводят к ухудшению течения НКИ, большему количеству смертельных исходов. Через год после инфекции у пациентов с СД2 и ВВГ чаще сохраняются жалобы, а ВВГ в большинстве случаев после инфекции нивелируется.

КЛЮЧЕВЫЕ СЛОВА: COVID-19; сахарный диабет 2-го типа; гипергликемия; летальность; предикторы.

BACKGROUND

Starting in the late 2019, the new coronavirus infection rapidly spread throughout the globe with high incidence and mortality and was eventually recognised as a pandemic by the World Health Organisation. Numerous studies showed that chronic cardiometabolic disorders are associated with more severe symptoms and an unfavourable prognosis both during COVID-19 and over long post-infection periods [1–3].

Diabetes is one of the diseases that may affect the course and the outcome of the infection caused by SARS-CoV-2. Diabetes is a common condition with its incidence steadily growing both in Russia and globally [4]. On 1 January 2022, the total count of diabetes patients in Russia was 4,871,863. Among them, 92.3% (4,500,000) had Type 2 diabetes mellitus (T2DM). However, if one includes the undiagnosed T2DM cases whose proportion in Russia is estimated at 54% on average, the real number of such patients may well be upwards of 10,000,000 (6.9% of the country's population) [5].

Numerous studies have shown that COVID-19 patients with diabetes will more often require hospital admission and non-invasive oxygen therapy and more often need transfer to intensive care wards and mechanical lung ventilation vs. those without carbohydrate metabolism disorders; their mortality rate is also higher [6, 7]. Moreover, clinical practice and literature indicate that a substantial portion of patients (10% to 60%) are first diagnosed with hyperglycaemia during in-patient care for COVID-19. In a post-COVID period, such newly diagnosed hyperglycaemia (NDH) may either subside or turn into diabetes with the causes and pathogenesis remaining obscure [8–10].

Given a high prevalence of carbohydrate metabolism disorders (CMDs) and existing data on their cross impact with COVID-19, it seems highly important to focus on studies whose design includes an assessment of not only the in-patient treatment but also the distant outcomes to improve results of preventive care and treatment and the patient's prognosis. This paper presents an analysis of a combined ACTIV & ACTIV 2 cohort fragment that spans over both peri-COVID and post-COVID treatment and follow-up periods.

OBJECTIVES

Analyse the correlation between CMDs, on the one hand, and mortality, course of disease, and distant effects, on the other, in COVID-19 patients; identify risk factors for unfavourable course of the disease.

MATERIALS AND METHODS

ACTIV and ACTIV 2 are multicentre non-interventional clinical practice registries that included patients who contracted COVID-19 between 29 June 2020 and 29 November 2020 (ACTIV) or between 1 October 2020 and 30 March 2021 (ACTIV 2).

The ACTIV registry consists of two non-overlapping branches, the out-patient and the in-patient ones. Both branches presupposed 6 visits: enrolment visit, visit on Days 7–12, outcome visit (discharge, hospital admission, death, etc.) and 3 follow-up visits at 3, 6, and 12 months after the hospital discharge. The ACTIV 2 registry contained in-patient data only and included 3 visits: enrolment visit, visit on Days 7–12, and outcome visit (discharge, hospital admission, death, etc.)

The design, justification, and statistical analysis of those studies have already been published [11]. Nosologic diagnosis was based on the ICD-10 criteria. In total, 6,396 patients

from the ACTIV registry and 2,968 patients from the ACTIV 2 registry were included in our sub-analysis. Within this sub-analysis, we identified three patient groups: Group 1 included CMD-free patients, 6,606 in total (70.5%); Group 2 included NDH patients (including those with newly diagnosed hyperglycaemia and those with pre-existing but undiagnosed T2DM), 1,073 in total (11.6%); Group 3 included T2DM patients, 1,611 in total (17.3%) (Table 1). It should be noted that within Group 2 we could not distinguish patients with newly diagnosed hyperglycaemia from those with pre-existing but undiagnosed T2DM, as the ACTIV and ACTIV 2 studies were observational in nature and lacked data on HbA1c levels for most of the patients. Hyperglycaemia was diagnosed based on venous plasma glucose ≥7.0 mmol/L [5]. It should be noted that our sub-analysis excluded several T1DM patients and those whose case resport forms did not contain any glucose levels which were entered on an "if any" basis.

Table 1. Characteristics of patients from ACTIV and ACTIV 2 registries.

Characteristic	Total cohort n=9,290	Group 1 CMD-free n=6,606	Group 2 NDH n=1,073	Group 3 T2DM n=1,611	P_{1-3}
Age	59 [48–68]	58 [46–67]	63 [55–71]	66 [59–73]	<0.001* P_{1-2}<0.001* P_{1-3}<0.001* P_{2-3}<0.001*
Females	4,947 (53.2%)	3,477 (52.2%)	533 (49.7%)	937 (58.2%)	<0.001*
Deceased	545 (5.9%)	259 (4.0%)	109 (10.4%)	177 (11.2%)	<0.001*
Overweight	2,921 (31.4%)	2,135 (39.0%)	331 (36.5%)	455 (34.2%)	<0.001*
Obesity, degree 1	1,700 (18.3%)	1,044 (19.1%)	251 (27.6%)	405 (30.4%)	
Obesity, degree 2	667 (7,2%)	379 (6,9%)	94 (10,4%)	194 (14,6%)	
Obesity, degree 3	296 (3,2%)	147 (2,7%)	39 (4,3%)	110 (83%)	
CT Score 1	3,136 (33.8%)	2,369 (45.5%)	291 (32.3%)	476 (34.5%)	<0.001*
CT Score 2	2,563 (27.6%)	1,695 (32.5%)	344 (38.2%)	524 (38.0%)	
CT Score 3	1,005 (10.8%)	579 (11.1%)	183 (20.3%)	243 (17.6%)	
CT Score 4	231 (2.5%)	108 (2.1%)	47 (5.2%)	76 (5.5%)	
SpO_2 75% to 94%	2,165 (23.3%)	1,334 (29.1%)	289 (45.2%)	542 (51.8%)	<0.001*
SpO_2 ≤75%	55 (0.6%)	21 (0.5%)	16 (2.5%)	18 (1.7%)	
Breathing rate 22 to 29	2,312 (24.9%)	1,448 (22.0%)	333 (31.4%)	531 (33.1%)	<0.001*
Breathing rate ≥30	178 (1.9%)	79 (1.2%)	33 (3.1%)	66 (4.1%)	
Body temperature 38.6 to 39.0°C	1,633 (17.6%)	1,114 (16.9%)	215 (20.2%)	304 (19.1%)	<0.001*
Body temperature >39.0°C	640 (6.9%)	431 (6.6%)	106 (10.0%)	103 (6.5%)	
Hypertension	5,289 (56.9%)	3,242 (48.7%)	701 (65.3%)	1,346 (83.6%)	<0.001*
Smokers	475 (5.1%)	369 (5.5%)	37 (3.4%)	69 (4.3%)	0.004*
Atrial fibrillation	672 (7.2%)	387 (5.8%)	100 (9.3%)	185 (11.5%)	<0.001*
Coronary artery disease	2,072 (22.3%)	1,195 (18.0%)	273 (25.4%)	604 (37.5%)	<0.001*
History of myocardial infarction	592 (6.4%)	324 (4.9%)	74 (6.9%)	194 (12.0%)	<0.001*
Chronic heart failure	1,595 (17.2%)	888 (13.3%)	220 (20.5%)	487 (30.2%)	<0.001*
History of stroke	401 (4.3%)	226 (3.4%)	49 (4.6%)	126 (7.8%)	<0.001*
T2DM	1,611 (17.3%)	0	0	1,611 (100%)	<0.001*
Chronic kidney disease	716 (7.7%)	381 (5.7%)	93 (8.7%)	242 (15.0%)	<0.001*
Chronic obstructive pulmonary disease	408 (4.4%)	272 (4.1%)	49 (4.6%)	87 (5.4%)	0.065
Asthma	321 (3.5%)	219 (3.3%)	40 (3.7%)	62 (3.8%)	0.467
Cancer at present	536 (5.8%)	372 (5.6%)	64 (6.0%)	100 (6.2%)	0.595
Anaemia	1,972 (21.2%)	1,282 (21.1%)	248 (23.2%)	442 (28.4%)	<0.001*

Notes: * statistically significant difference, p<0.05 (statistically significant difference between all 3 groups in Bonferroni corrected pairwise comparisons); in this and the following tables, data are presented as M [Q1; Q3], n (%).
CMD means Carbohydrate metabolism disorder; CT means Computer tomography; NDH means Newly diagnosed hyperglycaemia; SpO_2 means Peripheral capillary oxygen saturation; T2DM means Type 2 diabetes mellitus

The patients' median age was 59 [48; 68]; in the NDH Group: 63 [55; 71]; in the T2DM Group: 66 [59; 73]. Our analysis found that Group 2 (NDH) and Group 3 (T2DM) had significantly higher mortality — 109 (10.4%) and 177 (11.2%) cases, respectively, compared to Group 1 (CMD-free, 545 cases (5.8%)). Characteristics associated with more severe COVID-19 course, *i.e.*, CT Score 3 & CT Score 4 of pulmonary tissue damage, oxygen saturation under 94%, breathing rate over 22 per minute, body temperature ≥38.6°C, were more frequently found in Group 2 & Group 3. Moreover, these groups had a significantly higher rate of concomitant diseases such as hypertension, atrial fibrillation, history of stroke, coronary artery disease, chronic heart failure, chronic kidney disease, and anaemia vs. Group 1 patients (CMD-free ones). The highest rate; of these concomitant diseases was observed in Group 3 (the difference is significant).

Our sub-analysis of combined ACTIV & ACTIV 2 registries presents the findings in patients with newly diagnosed and prior hyperglycaemia and an analysis of the impact of CMD on the COVID-19 course and outcome.

Statistical analysis

We analysed the data in IBM SPSS STATISTICS 26 software. Kolmogorov-Smirnov test was applied to verify normal distribution. Kruskal-Wallis test for independent samples was applied to analyse quantitative data with other-than-normal distribution in the three samples. Pearson's chi-squared test or Fisher's exact test (depending on the minimum estimated value) was applied to analyse qualitative parameters in two patient groups. For parameters showing significant differences, the odds value was derived with a 95% confidence interval (CI), and the degree of association between nominal variables was assessed. To analyse nominal parameters in the three groups, we used multiple-field contingency tables and post-hoc analysis. Cochran's Q test was applied to comparisons of nominal parameters across the three related populations. Using binary logistic regression, we developed a predictive model to assess the risk of a lethal outcome in relation to age, glycaemia level, myocardial infarction history, history of stroke, or concomitant coronary artery disease. Odds ratios with a 95% confidence interval for the predictors exerting statistically significant impact on the outcome are presented as a forest plot. Cut-off values for logistic regressions (p) were determined through ROC curves.

FINDINGS

Body mass index (BMI) in NDH patients (Group 2) and T2DM patients (Group 3) was significantly higher vs. those in Group 1 (see Table 2). A BMI under 30 kg/m^2 was more common for Group 1 (CMD-free) patients (p<0.001). The study groups showed significant differences in their mortality rate (p<0.001): the number of deceased patients in Group 2 (109 cases, 10.4%) and Group 3 (177 cases, 11.2%) was higher than in Group 1 (254 cases, 2.9%). The study groups showed significant differences (p<0.001) in CT score reflecting the degree of pulmonary involvement and the severity of COVID-19-induced pneumonia. We found Group 2 and Group 3 to have 1.5 to 2 times higher rate of CT score 3 and CT score 4 (183 [20.3%] and 47 [5.2%] cases, respectively, within Group 2; 243 [17.6%] and 76 [5.5%] cases, respectively, within Group 3) as compared to Group 1 (CMD-free) (574 [11.1%] and 106 [2.0%] cases, respectively). C-reactive protein ≥50 mg/L and SpO_2 ≤ 90% were significantly more frequently observed in Group 2 and Group 3 vs. CMD-free group. More glucocorticosteroid prescriptions were issued for Group 2 than the other groups (p<0.001).

Significant differences were discovered when comparing the association between mortality rates and NDH or T2DM (p<0.001). Thus, the odds of death were 2.48 times higher in T2DM patients (95% CI 2.05–3.00) and 2.04 times higher in those with NDH (95% CI 1.64–2.55). While Group 1 (CMD-free) patients did also show significant difference in mortality rate, their overall odds of death, were, conversely, 2.94 times lower (95% CI 0.28–0.40), as presented on Figure 1.

Moderate and severe COVID-19 patients with peripheral capillary oxygen saturation under 93% were a cohort of special interest (see Table 3). This cohort had the highest mortality rate, distributed across the patient groups as follows: 21.4% for NDH (Group 2) patients; 20.2% for T2DM (Group 3) patients; and 12.4% for Group 1 patients; these differences are significant (p<0.001). NDH patients needed corticosteroid therapy more often than others (41 cases [24.0%]), whereas in the other groups this therapy was prescribed to patients in under 14.1% of cases (p=0.006).

Post-discharge symptoms are a serious cause of post-COVID health-related quality of life deterioration; this is why the medical community came up with a concept of post-COVID syndrome. In the ACTIV registry, follow-up was conducted at 3, 6, and 12 months after discharge. In that period, most of the symptoms reported by the patients were: decreased sensation of taste, cough, expectorations, myalgia, thoracalgia, heart palpitations, high blood pressure, fatigue, diarrhoea, rhinitis, conjunctivitis, throat irritation, and high body temperature (see Table 4). Groups 2 and 3 showed significantly higher rates and longer periods of decreased sensation of taste (p_{total}<0.001), cough (p_{total}<0.001), expectorations (p_{total}<0.001), myalgia (p_{total}<0.001), thoracalgia (p_{total}<0.001), heart palpitations (p_{total}<0.001), high blood pressure (p_{total}<0.001), and fatigue (p_{total}<0.001).

During COVID-19, all Group 3 patients and 87% of Group 2 patients were receiving antihyperglycaemic therapy. Based on the widespread practice, insulin therapy was a key tool of hyperglycaemia control across both patient groups during the acute phase of COVID-19 [12]; however, no significant differences were identified in the type of antihyperglycaemic therapy and a tendency towards shifting to oral sugar-reducing drugs in the T2DM group was observed (see Table 5).

After 12 months, only 18 Group 2 patients (1.7%) were receiving antihyperglycaemic treatment in the form of oral-administered single-drug therapy. In Group 3, the nature of antihyperglycaemic treatment changed by 12 months after discharge. The proportion of those on oral-administered single-drug therapy reached 72.6%, whereas 18.9% were receiving a dual combined oral-administered drug therapy, and the proportion of patients who controlled their T2DM through basal insulin + oral-administered drugs amounted to 8.5% only.

We developed a predictive model to assess the risk of death in relation to age, glycaemia level, coronary artery disease, myocardial infarction history, or stroke history. A univariate analysis revealed that all these variables had

Table 2. Analysis of certain parameters across the study groups

Parameter	Group 1 CMD-free n=6,606	Group 2 NDH n=1,073	Group 3 T2DM n=1,611	P
BMI				
Me [Q1–Q3]	27.1 [24.2–30.5]	28.8 [25.6–32.7]	30.4 [27.0–34.6]	<0.001*
Under 18.5	58 (1.1%)	7 (0.8%)	6 (0.5%)	<0.001*
18.5 to 24.9	1,696 (31.2%)	186 (20.5%)	162 (12.2%)	
25 to 29.9	2,124 (39.1%)	331 (36.5%)	455 (34.2%)	
30 to 34.9	1,035 (19.1%)	251 (27.6%)	405 (30.4%)	
35 to 39.9	376 (6.9%)	94 (10.4%)	194 (14.6%)	
40 and over	144 (2.7%)	39 (4.3%)	110 (8.3%)	
Mortality				
Alive	6,254 (96.1%)	944 (89.6%)	1,406 (88.8%)	<0.001*
Deceased	254 (3.9%)	109 (10.4%)	177 (11.2%)	
Odds ratio (95% CI)	0.34 (0.28–0.40)	2.04 (1.64–2.55)	2.48 (2.05–3.00)	
p	<0.001*	<0.001*	<0.001*	
CT score				
CT score 3	574 (11.1%)	183 (20.3%)	243 (17.6%)	<0.001*
CT score 4	106 (2.0%)	47 (5.2%)	76 (5.5%)	
C-reactive protein ≥50 mg/L				
No	3,796 (77.7%)	589 (68.0%)	808 (63.9%)	<0.001*
Yes	1,088 (22.3%)	277 (32.0%)	456 (36.1%)	
Corticosteroid therapy				
Not prescribed	5,735 (86.8%)	808 (75.3%)	1,356 (84.2%)	<0.001*
Prescribed	871 (13.2%)	265 (24.7%)	255 (15.8%)	
SpO_2 ≤ 90%				
No	4,298 (94.4%)	554 (86.1%)	885 (84.6%)	<0.001*
Yes	253 (5,6%)	86 (13,4%)	161 (15,4%)	

Notes: * significant difference (p<0.05)
p<0.001* on pairwise comparisons between all groups; BMI, body mass index; CT, computed tomography.

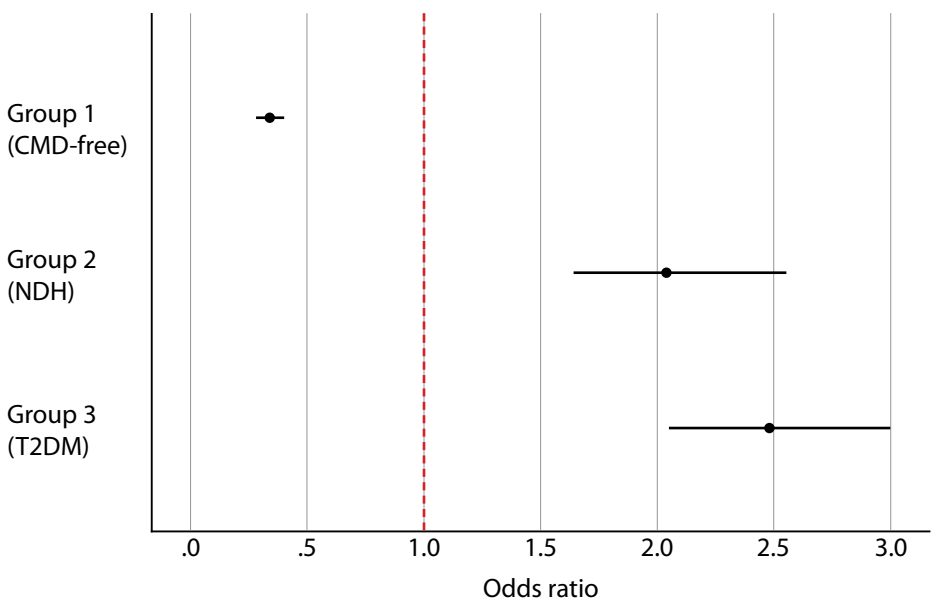

Figure 1. Odds ratio (95% CI) of a lethal outcome depending on the nature of carbohydrate metabolism disorder

Table 3. Comparison of mortality and corticosteroid therapy in patients with SpO_2 < 93% across the study groups

Parameter	Group 1 CMD-free n=6,606	Group 2 NDH n=1,073	Group 3 T2DM n=1,611	P
Mortality				
Recovered	829 (87.9%)	173 (78.6%)	343 (79.8%)	<0.001*
Deceased	114 (12.1%)	47 (21.4%)	87 (20.2%)	
Corticosteroid therapy				
Not prescribed	638 (85.9%)	130 (76.0%)	319 (86.9%)	0.006*
Prescribed	105 (14.1%)	41 (24.0%)	48 (13.1%)	

Note: * significant difference (p<0.05)

a significant impact on the odds of death. It is important to note that a BMI > 30 kg/m^2 or high blood pressure *per se*, when adjusted on other factors, did not significantly affect the odds of death and rose to significance only when associated with the aforementioned predictors.

Likewise, a multivariate analysis revealed all factors in question to be significantly affecting the odds of death. Their characteristics are presented in Table 6.

The observed relationship can be described as Equation (1):

$$\mathbf{P = 1 / (1 + e^{-z}) \times 100\% \ (1)}$$

$$z = - 7.95 + 0.06 \times X_{age} + 0.12 \times X_{glycaemia} + 0.48 \times X_{MIH} + 0.34 \times X_{CAD} + 0.76 \times X_{SH},$$

where P is the odds of death (%); X_{age} is age (years); $X_{glycaemia}$ is glycaemia level (mmol/L); X_{MIH} is myocardial infarction history (no = 0; yes = 1); X_{CAD} is coronary artery disease (no = 0; yes = 1); and X_{SH} is history of stroke (no = 0; yes = 1).

Table 4. Most frequent self-reported symptoms reported across the study groups after discharge at 3, 6, and 12-month

Symptom	Patient group	Follow-up after			p
		3 months	6 months	12 months	
Decreased/lost sensation of taste	Group 1 (CMD-free)	82 (1.2%)	37 (0.6%)	15 (0.2%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}=0.006*
	Group 2 (NDH)	20 (1.9%)	10 (0.932%)	2 (0.186%)	<0.001* p_{3-6}=0.008* p_{3-12}<0.001* p_{6-12}=0.109*
	Group 3 (T2DM)	9 (0.559%)	6 (0.372%)	4 (0.248%)	0.895
	p (between the groups at each phase)	0.009*	0.161	0.846	
Cough	Group 1 (CMD-free)	209 (3.1%)	102 (1.5%)	51 (0.8%)	<0.001* p_{3-6}=0.001* p_{3-12}<0.001* p_{6-12}=0.003*
	Group 2 (NDH)	38 (3.5%)	15 (1.4%)	9 (0.839%)	0.031* p_{3-6}=0.064* p_{3-12}=0.011* p_{6-12}=0.487*
	Group 3 (T2DM)	55 (3.4%)	25 (1.6%)	13 (0.807%)	0.005* p_{3-6}=0.021* p_{3-12}=0.002* p_{6-12}=0.401*
	p (between the groups at each phase)	0.066	0.752	0.643	
Expectorations	Group 1 (CMD-free)	47 (0.7%)	17 (0.3%)	8 (0.1%)	<0.001* p_{3-6}=0.002* p_{3-12}<0.001* p_{6-12}=0.439*
	Group 2 (NDH)	11 (1.0%)	5 (0.466%)	2 (0.186%)	0.066
	Group 3 (T2DM)	9 (0.559%)	8 (0.497%)	6 (0.372%)	0.407
	p (between the groups at each phase)	0.288	0.104	0.029*	

Table 4 continued

Symptom	Patient group	Follow-up after			p
		3 months	6 months	12 months	
Myalgia	Group 1 (CMD-free)	80 (1.2%)	40 (0.6%)	20 (0.3%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}=0.312*
	Group 2 (NDH)	17 (1.6%)	11 (1.0%)	4 (0.373%)	0.047* p_{3-6}=0.358* p_{3-12}=0.014* p_{6-12}=0.126*
	Group 3 (T2DM)	28 (1.7%)	9 (0.559%)	13 (0.807%)	0.296
	p (between the groups at each phase)	0.015*	0.191	0.002*	
Thoracalgia	Group 1 (CMD-free)	102 (1.5%)	56 (0.8%)	27 (0.4%)	0.013* p_{3-6}=0.291* p_{3-12}=0.004* p_{6-12}=0.064*
	Group 2 (NDH)	19 (1.8%)	14 (1.3%)	4 (0.373%)	0.025* p_{3-6}=0.373* p_{3-12}=0.008* p_{6-12}=0.075*
	Group 3 (T2DM)	39 (2.4%)	33 (2.0%)	17 (1.1%)	0.349
	p (between the groups at each phase)	0.001*	<0.001*	<0.001*	
Heart palpitations	Group 1 (CMD-free)	233 (3.5%)	140 (2.1%)	62 (0.9%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}=0.012*
	Group 2 (NDH)	47 (4.4%)	30 (2.8%)	18 (1.7%)	0.018* p_{3-6}=0.099* p_{3-12}=0.005* p_{6-12}=0.239*
	Group 3 (T2DM)	65 (4.0%)	25 (1.6%)	22 (1.4%)	0.008* p_{3-6}=0.003* p_{3-12}=0.018* p_{6-12}=0.584*
	p (between the groups at each phase)	0.005*	0.104	0.004*	
High blood pressure	Group 1 (CMD-free)	425 (6.4%)	369 (5.5%)	201 (3.0%)	0.047* p_{3-6}=0.828* p_{3-12}=0.043* p_{6-12}=0.025*
	Group 2 (NDH)	74 (6.9%)	64 (6.0%)	33 (3.1%)	0.109
	Group 3 (T2DM)	126 (7.8%)	118 (7.3%)	48 (3.0%)	0.041* p_{3-6}=0.593* p_{3-12}=0.061* p_{6-12}=0.016*
	p (between the groups at each phase)	<0.001*	<0.001*	0.381	

End of table 4

Symptom	Patient group	Follow-up after			p
		3 months	6 months	12 months	
Fatigue	Group 1 (CMD-free)	699 (10.5%)	412 (6.2%)	209 (3.1%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}<0.001*
	Group 2 (NDH)	125 (11.6%)	65 (6.1%)	32 (3.0%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}=0.017*
	Group 3 (T2DM)	193 (12.0%)	136 (8.4%)	74 (4.6%)	<0.001* p_{3-6}=0.004* p_{3-12}<0.001* p_{6-12}=0.017*
	p (between the groups at each phase)	<0.001*	<0.001*	<0.001*	
Diarrhoea	Group 1 (CMD-free)	32 (0.5%)	9 (0.1%)	8 (0.1202%)	0.001* p_{3-6}=0.001* p_{3-12}=0.004* p_{6-12}=0.655*
	Group 2 (NDH)	7 (0.652%)	2 (0.186%)	2 (0.186%)	0.607
	Group 3 (T2DM)	7 (0.435%)	3 (0.186%)	6 (0.372%)	0.497
	p (between the groups at each phase)	0.568	0.731	0.029*	
Rhinitis	Group 1 (CMD-free)	27 (0.4%)	14 (0.2%)	6 (0.902%)	0.037* p_{3-6}=0.136* p_{3-12}=0.011* p_{6-12}=0.286*
	Group 2 (NDH)	5 (0.466%)	6 (0.559%)	1 (0.093%)	0.121
	Group 3 (T2DM)	6 (0.372%)	1 (0.062%)	3 (0.186%)	0.549
	p (between the groups at each phase)	0.842	0.023*	0.388	
Conjunctivitis	Group 1 (CMD-free)	3 (0.045%)	0	2 (0.03%)	0.368
	Group 2 (NDH)	0	0	0	-
	Group 3 (T2DM)	2 (0.124%)	0	0	-
	p (between the groups at each phase)	0.240	-	0.710	
Throat irritation	Group 1 (CMD-free)	40 (0.6%)	17 (0.3%)	9 (0.135%)	<0.001* p_{3-6}=0.001* p_{3-12}<0.001* p_{6-12}=0.695*
	Group 2 (NDH)	7 (0.652%)	4 (0.373%)	1 (0.093%)	0.325
	Group 3 (T2DM)	7 (0.435%)	0	2 (0.124%)	0.066
	p (between the groups at each phase)	0.812	0.099	0.951	
High body temperature	Group 1 (CMD-free)	51 (0.8%)	16 (0.2%)	5 (0.075%)	<0.001* p_{3-6}<0.001* p_{3-12}<0.001* p_{6-12}=0.262*
	Group 2 (NDH)	5 (0.466%)	3 (0.280%)	2 (0.186%)	0.417
	Group 3 (T2DM)	4 (0.248%)	1 (0.062%)	4 (0.248%)	0.325
	p (between the groups at each phase)	0.146	0.405	0.069	

Table 5. Antihyperglycaemic therapy in Group 2 and Group 3 during COVID-19 treatment

Therapy	Group 2 NDH n=1,073	Group 3 T2DM n=1,611	P
Oral sugar-reducing drugs	323 (30.1%)	626 (38.9%)	<0.001*
Basal insulin therapy + oral sugar-reducing drugs	216 (20.1%)	368 (22.8%)	0.096
Basal-bolus insulin therapy	395 (36.8%)	617 (38.3%)	0.437

Note: * significant difference (p<0.05)

Table 6. Factors confirmed by a multivariate analysis to be affecting the odds of death

Predictor	Crude odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p
1 year age increment	1.08 [1.07–1.09]	<0.001*	1.07 [1.06–1.08]	<0.001*
1 mmol/L glycaemia level increment	1.14 [1.11–1.16]	<0.001*	1.12 [1.1–1.15]	<0.001*
History of myocardial infarction	3.7 [2.92–4.69]	<0.001*	1.62 [1.22–2.16]	0.001*
Coronary artery disease	3.9 [3.28–4.66]	<0.001*	1.4 [1.12–1.76]	0.004*
History of stroke	4.80 [3.70–6.22]	<0.001*	2.14 [1.58–2.90]	<0.001*

Note: * A factor significantly affecting the odds of death (p < 0.05).

The regression model we derived is statistically significant (p<0.001). Based on the value of the Nigelkirk's determination coefficient, Model 1 takes into account 18.6% of the factors that determine the odds of death.

Based on the regression coefficient values, age, glycaemia level, myocardial infarction history, coronary artery disease, and stroke history are directly related to the odds of death. A 1-year age increment increases the odds of death by 1.07 times (95% CI 1.06–1.08); a 1-mmol/L glycaemia level increment, by 1.12 times (95% CI 1.1–1.15); history of myocardial infarction, by 1.62 times (95% CI 1.22–2.16); coronary artery disease, by 1.40 times (95% CI 1.12–1.76), and history of stroke, by 2.14 times (95% CI 1.58–2.90). Figure 2 presents the impact on the odds of death (95% CI) for each of the factors included in Model 1.

Logistic regression cut-off value P was determined through ROC curves analysis. The resulting curve is presented on Figure 3.

The area under the ROC curve (which represents the relationship between the odds of death and the value of the logistic regression) amounts to 0.786±0.01 (95% CI 0.77–0.81). The cut-off value of logistic regression is 0.061. Any value of the regression that is equal of higher than this cut-off value means a high risk of a lethal outcome. Values under 0.061 mean a low risk of a lethal outcome. At this cut-off value, Model 1 has 72.2% sensitivity and 68.5% specificity.

DISCUSSION

Our sub-analysis of the combined ACTIV and ACTIV 2 real clinical practice registries which included COVID-19 out-patients, in-patients and their 12-month post-COVID follow up aimed to determine the impact of hyperglycaemia on the COVID-19 outcome. Relevance of this study stems from the fact that many researchers consider carbohydrate

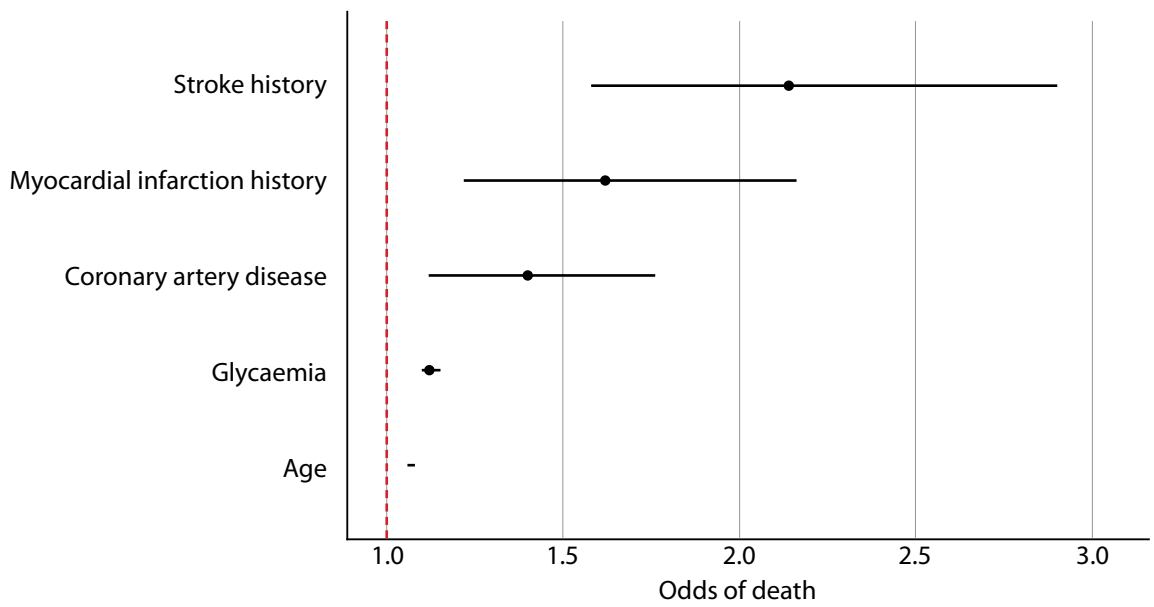

Figure 2. Impact on the odds of death (95% CI) for each of the studied predictors

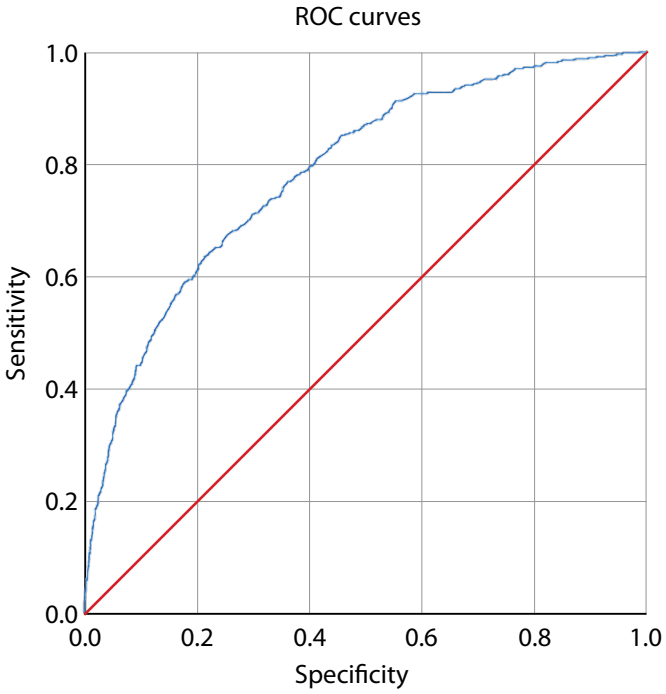

Figure 3. ROC curve showing the relationship between the odds of death and the value of predictive function (1)

metabolism disorder to be a major risk factor of more severe COVID-19 course and of the unfavourable outcomes [1, 7, 9, 13].

Our analysis found the incidence of hyperglycaemia in COVID-19 patients within the study cohort to be 28.9%, where 11.6% were NDH patients with no prior CMD history, and the remaining 17.3% were T2DM patients.

As per our sub-analysis, mortality rate in hyperglycaemia patients was 10.6%, *i.e.*, significantly higher than that in CMD-free patients (3.9%); T2DM patients had significantly higher mortality rate than NDH patients (11.2% vs. 10.4%). A similar trend was observed in patients with respiratory deficiency (SpO_2 < 93%), among whom NDH or T2DM doubled the odds of death.

Our findings regarding vulnerability of SARS-CoV-2-infected patients with hyperglycaemia correlate with findings from multiple studies in Russia and other countries that report 2 to 3 times higher mortality in diabetes patients vs. those without diabetes. Thus, a French nationwide CORONADO study found mortality rate in T2DM patients to be 20.6% [14]; a similar study conducted in the USA determined it at 28.8% [15]; another one conducted in the UK found it at 30.1% [16]; according to Russian Federal Registry of Diabetes, that mortality rate is 15.2% [13].

Based on our sub-analysis of the combined ACTIV and ACTIV 2 registries, one may conclude that CMD implies a more severe COVID-19 course of disease. This is also confirmed by significantly higher incidence of CT score 3 and CT score 4 patients among the T2DM and NDH groups and more acute immunoinflammatory syndrome in such patients vs. those CMD-free.

This relationship correlates with findings of our colleagues from other countries: a meta-analysis of 47 studies showed that diabetes is associated with greater severity of COVID-19 course of disease (odds ratio higher by 2.20 times; 95% CI 1.69–2.86; p<0.00001) and higher mortality rate (odds ratio higher by 2.52 times; 95% CI 1.93–3.30; p<0.00001) [17]. A meta-analysis of 16 studies showed that patients with prior T2DM ran a higher risk of severe COVID-19 course (odds ratio higher by 2.60 times; 95% CI 1.96–3.45; p=0.01) [18]. A combined analysis of 33 studies found a significant relationship between T2DM and greater severity of the infection course (odds ratio higher by 2.75 times; 95% CI 2.09–3.62; p<0.01) and higher mortality rate in COVID-19 (combined odds ratio higher by 1.90 times; 95% CI 1.37–2.64; p<0.01) [19].

Interestingly, CMDs affect the mortality rate in COVID-19 differently, depending on the disorder type. In our study, T2DM increased the odds of death by 2.48 times, whereas NDH did so by 2.04 times only. Conversely, CMD-free status decreased the odds of death by 2.94 times. Likewise, NDH patients had more unfavourable COVID-19 course of disease vs. CMD-free ones; however, T2DM patients were not comparable to NDH patients by clinical laboratory tests and degree of pulmonary involvement.

This finding runs against many researchers' claim that NDH causes more unfavourable course and prognosis in COVID-19 vs. a pre-existing T2DM [10, 20–22]. It seems that a deviation from that pattern was detected in our case due to the limitations of our observational study wherein patients having a stress-induced or steroid-induced hyperglycaemia could not be distinguished from those with undiagnosed T2DM.

It is important that our findings show peri-COVID CMDs to affect the course of longer-term post-COVID period. Our sub-analysis of the combined ACTIV and ACTIV 2 registries revealed that CMD patients reported greater numbers of negative symptoms and longer periods over which they were experienced in post-COVID phase. Thus, at 12 months after COVID-19 T2DM patients were experiencing expectorations, thoracalgia, heart palpitations, high blood pressure, fatigue, and diarrhoea significantly more frequently vs. CMD-free patients. The same symptoms, except thoracalgia and fatigue, were reported by NDH patients who experienced them more frequently than CMD-free patients, but less frequently than T2DM ones. These findings will help adjust post-COVID rehabilitation programmes, as NDH and T2DM patients should be considered a high-risk group for more prolonged and persisting post-COVID complains [23]. Unfortunately, we could not analyse post-COVID mortality due to the low response rate. However, other studies show that diabetes is one of the early independent predictors of 90-day mortality in a sample of 4,643 severe COVID-19 patients [24]; T2DM in patients over 60 increases the odds of death within 90 days (odds ratio higher by 2.55 times; 95%CI 1.16–5.61; p=0.016) [25]. An analysis of over 100,000 hospitalized COVID-19 patients in the USA shows diabetes to increase by 20% the odds of a hospital readmission within six months [26].

Our substantial finding is high incidence of concomitant diseases in CMD patients. A multivariate analysis revealed co-morbid conditions such as coronary artery disease, myocardial infarction history, or stroke history to substantially increase the odds of death (by 1.4, 1.6, and 2.1 times, respectively). Interestingly, our sub-analysis did not confirm obesity or hypertension to increase the odds of death (such relationship was reported by some studies: [7, 27]) unless associated with the above conditions.

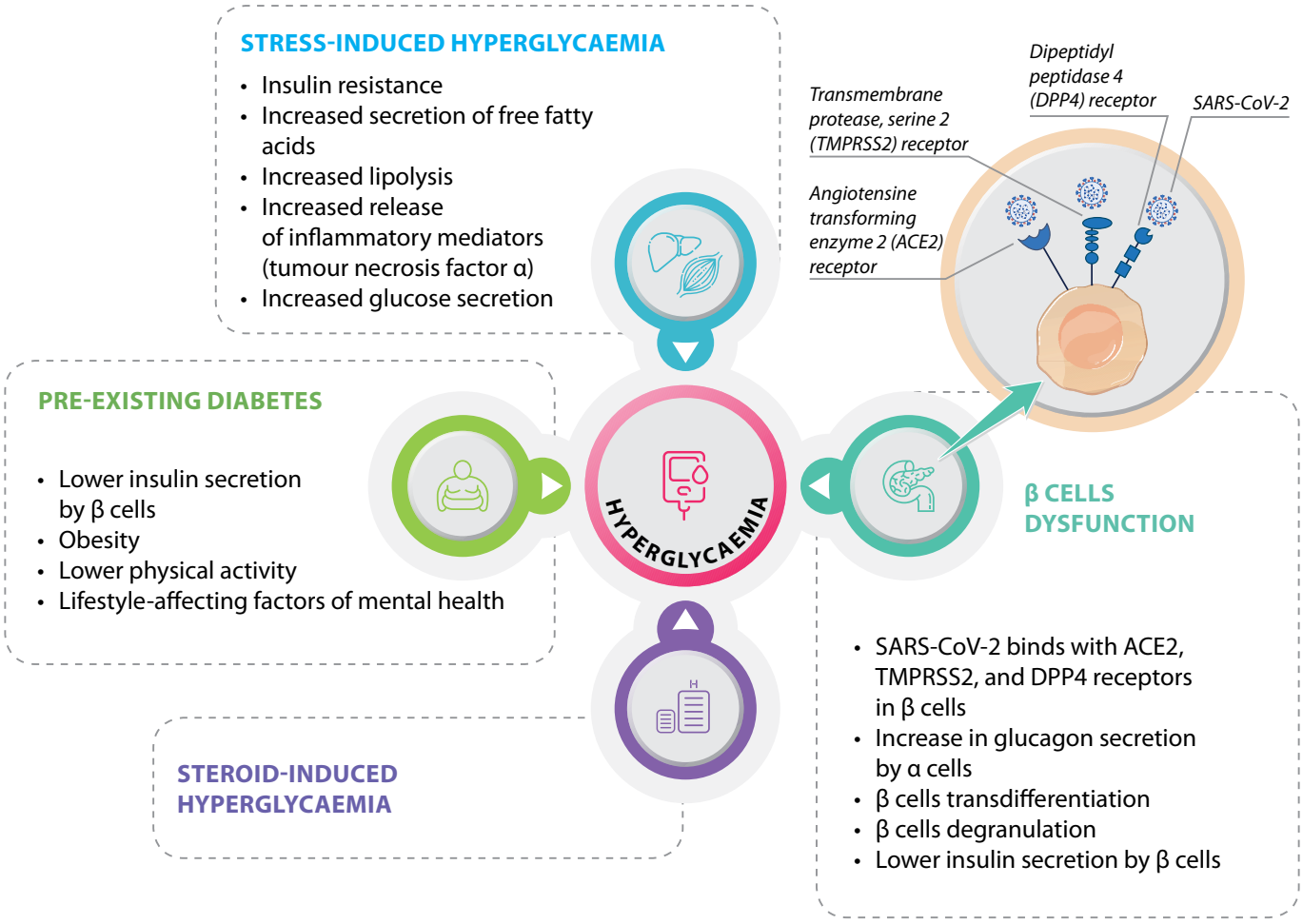

Figure 4. Probable mechanisms of development of newly diagnosed hyperglycaemia/diabetes in COVID-19 patients. Adapted from [31]

Significance of co-morbid diseases in T2DM patients was shown in prior studies based on an analysis of the ACTIV registry. In combination with obesity and cardiovascular diseases (CVDs), diabetes significantly increased the risk of death for hospital patients during the acute COVID-19 phase (odds ratio higher by 2.24 times; 95% CI 1.59–3.15; p<0.01 across all age groups; odds ratio higher by 2.51 times; 95% CI 1.69–3.72; p<0.01 for patients over 60). A significant increase in the odds of death was also observed for the combinations "hypertension + obesity + diabetes" and "hypertension + coronary artery disease + chronic heart failure + diabetes" (odds ratio higher by 2.17 times; 95% CI 1.53–3.08; p<0.01, and odds ratio higher by 4.21 times; 95% CI 2.78–6.38; p<0.01, respectively) [3, 28]. Interestingly, average blood sugar was found to vary depending on whether the patients had any co-morbid conditions and on the number of such conditions in a patient: 5.44 mmol/L for CVD-free patients; 6.07 mmol/L for those with one CVD; 7.1 mmol/L for those with two or three CVDs, and 7.79 mmol/L for those with four or more CVDs (p<0.01) [3].

A key objective of our study was to analyse the incidence of newly diagnosed CMDs among COVID-19 patients and to assess the nature and persistence of such CMDs. Our sub-analysis found peri-COVID NDH (11.6% rate) to result in 1.7% of newly diagnosed cases of T2DM controlled by oral sugar-reducing drugs at 12 month follow-up. This shows a transitory nature of peri-COVID hyperglycaemia. However, given the negative impact of hyperglycaemia on COVID-19 course of disease and outcome, this condition requires early diagnostics and serious timely correction efforts.

The incidence of new cases of diabetes during recovery from COVID-19 has been a focus of many studies. Such studies are complexified by extremely heterogeneous cohorts for studying the incidence of COVID-19, given the differences in COVID-19 course of disease, gender and ethnic characteristics of patient samples, differences in SARS-CoV-2 variants prevailing during various phases of the COVID-19 pandemic, and differences in the application of corticosteroid therapy [29]. Perhaps, this is the reason why very few studies have attempted to analyse NDH outcomes in long-term post-COVID period; this highlights the need for more such studies. A distinctive study by W. Rathmann *et al*. ([30]) should be mentioned in this regard: based on an analysis of a 8.8-million-patient database, these scholars compared the rate of new T2DM cases diagnosed after COVID-19 against the rate of new diabetes cases diagnosed after acute respiratory diseases in general and found that COVID-19 results in 28% higher rate of newly diagnosed T2DM; we are making a similar point in this paper.

The literature suggests quite a few hypotheses on probable mechanisms of pathological interaction between SARS-CoV-2 and CMDs. Exact underlying processes remain obscure; however, one may presuppose a number of complex cross impact pathways, including direct damage of the pancreas cells resulting in lower insulin secretion; acute inflammation resulting in higher insulin resistance;

stress-induced hyperglycaemia; and negative effects of corticosteroid therapy resulting in steroid-induced hyperglycaemia (see Figure 4).

Thus, the interaction between COVID-19 and diabetes can be described as a two-way relationship of between the infection process and CMDs. A better understanding of this relationship and timely preventive care will help minimise the impact of this harmful tandem on the prognosis both during the current pandemic and during any future one.

Limitations of this study

ACTIV and ACTIV 2 are real medical practice registries. Some of the variables were entered therein on an "if any" basis; the respective fields were not mandatory to fill out. Thus, some data were lost at the stage of data entry by medical researchers; moreover, the accuracy of data transmitted orally by phone may be limited. Also, several changes in federal clinical guidance for COVID-19 treatment took place during the data collection periods (most of the changes concerned the management of COVID-19 patients and the respective therapy). It should be noted that, due to lack of information about COVID-19 at the outset of the pandemic (spring and summer 2020), the actual number of hospital admissions for SARS-CoV-2 infection exceeded the number justified by immediate medical indications; thus, it may be surmised that the patients entered in the registry had various degrees of COVID-19 severity.

CONCLUSION

This paper presents a sub-analysis of the combined ACTIV and ACTIV 2 registries. To date, this is one of the most large-scale studies (spanning over 9,000 patients) of CMDs impact on COVID-19 outcome. An important feature of this study is that it includes not only an analysis of NDH and T2DM impact on COVID-19 course and mortality in peri-COVID period but also over longer-term post-COVID outcomes (at 12 months).

Our analysis revealed that CMDs increase the severity of COVID-19, higher degree of pulmonary tissue damage, greater respiratory deficiency, and more acute immunoinflammatory syndrome. We showed that a peri-COVID hyperglycaemia (NDH + T2DM) increases the odds of death by 20%, and the predictors of a lethal outcome include co-morbid conditions such as coronary artery disease, myocardial infarction history, stroke history, and higher age.

At one year post-COVID, NDH and T2DM patients report symptoms typical for post-COVID syndrome more often than CMD-free patients; following the acute phase of COVID-19, NDH turns into 1.7% of new T2DM cases.

DISCLOSURES

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Authors' contribution. Vladimir V. Salukhov: study concept and design; results generation and interpretation; manuscript drafting. Gregory P. Arutyunov: study concept and design; results generation and interpretation. Ekaterina I. Tarlovskaya: study concept and design; results generation and interpretation. Tatiana I. Batluk: results generation and interpretation; manuscript drafting. Roman A. Bashkinov: results generation and interpretation; manuscript drafting. Irina V. Samus: statistical analysis of data; results interpretation; manuscript drafting. Evgeniy S. Melnikov: results generation and interpretation. Marina A. Trubnikova: results generation and interpretation. Alexander G. Arutyunov: study concept and design; results generation and interpretation; manuscript corrections.

Every author has approved the final version of the text prior to publication and agreed to accept responsibility for all aspects of this study, which implies due investigation and resolution of any issue related to the accuracy or integrity of any part thereof.

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