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Post-COVID-19 syndrome and diabetes mellitus: a propensity-matched analysis of the International HOPE-II COVID-19 Registry

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Background: Diabetes mellitus (DM) is one of the most frequent comorbidities in patients suffering from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a higher rate of severe course of coronavirus disease (COVID-19). However, data about post-COVID-19 syndrome (PCS) in patients with DM are limited.

Methods: This multicenter, propensity score-matched study compared long-term follow-up data about cardiovascular, neuropsychiatric, respiratory, gastrointestinal, and other symptoms in 8,719 patients with DM to those without DM. The 1:1 propensity score matching (PSM) according to age and sex resulted in 1,548 matched pairs.

Results: Diabetics and nondiabetics had a mean age of 72.6 ± 12.7 years old. At follow-up, cardiovascular symptoms such as dyspnea and increased resting heart rate occurred less in patients with DM (13.2% vs. 16.4%; p = 0.01) than those without DM (2.8% vs. 5.6%; p = 0.05), respectively. The incidence of newly diagnosed arterial hypertension was slightly lower in DM patients as compared to non-DM patients (0.5% vs. 1.6%; p = 0.18). Abnormal spirometry was observed more in patients with DM than those without DM (18.8% vs. 13; p = 0.24). Paranoia was diagnosed more frequently in patients with DM than in non-DM patients at follow-up time (4% vs. 1.2%; p = 0.009). The incidence of newly diagnosed renal insufficiency was higher in patients suffering from DM as compared to patients without DM (4.8% vs. 2.6%; p = 0.09). The rate of readmission was comparable in patients with and without DM (19.7% vs. 18.3%; p = 0.61). The reinfection rate with COVID-19 was comparable in both groups (2.9% in diabetics vs. 2.3% in nondiabetics; p = 0.55). Long-term mortality was higher in DM patients than in non-DM patients (33.9% vs. 29.1%; p = 0.005).

Conclusions: The mortality rate was higher in patients with DM type II as compared to those without DM. Readmission and reinfection rates with COVID-19 were comparable in both groups. The incidence of cardiovascular symptoms was higher in patients without DM.

KEYWORDS

diabetes mellitus, post-COVID-19 syndrome, SARS-CoV-2, respiratory complications, reinfection, vaccination rate, long-term mortality

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with significant morbidity and mortality (1).

Among other related diseases such as arterial hypertension and obesity, diabetes mellitus (DM) is identified as a risk factor for the severe course of COVID-19, developing sepsis, and mortality (2–4).

In patients suffering from COVID-19, SARS-CoV-2 binds the angiotensin-converting enzyme 2 (ACE2) receptor and uses it as a potential target for viral interventions (5). In diabetic mice, the expression of ACE2 is increased as compared to mice without DM. In addition, patients who suffered from insufficient glycemic control showed worse outcomes, such as more complications and higher mortality rates (6). New-onset DM and metabolic complications in patients suffering from manifested DM with high doses of insulin have been revealed in COVID-19 (7, 8). Furthermore, uncontrolled glycemic levels in DM patients cause organ injury and may be exacerbated in patients suffering from COVID-19 (9).

The international Health Outcome Predictive Evaluation for COVID-19 (HOPE COVID-19) Registry was initiated to investigate comorbidity and mortality of COVID-19 (10). In the Health Outcome Predictive Evaluation for COVID-19 II (HOPE-II COVID-19) Registry, we investigated readmission, reinfection, vaccination rate, cardiovascular, neuropsychiatric, respiratory, gastrointestinal, and other symptoms in hospitalized patients suffering from COVID-19 and concomitant DM type II. Complications related to COVID-19 and long-term mortality were also systematically analyzed.

Material and methods

Study design and participants

HOPE-II COVID-19 (NCT04334291) is an international project at 55 international centers. It is designed as a retrospective and prospective cohort registry to investigate post-COVID-19 syndrome without any conflict of interest. We included hospitalized patients with a confirmed diagnosis of COVID-19. There are no exclusion criteria, except for the patient's explicit refusal to participate. Initially, data on 8,828 hospitalized patients suffering from COVID-19 were

collected until 30th September 2021. In this study, we excluded 56 patients due to age <18 and 53 patients with DM type I. Data from 8,719 consecutive patients with COVID-19 regarding their concomitant DM type II status were analyzed.

Ethics approval

This study was executed in compliance with the Declaration of Helsinki regarding human subjects, and the study was approved by the center ethics committee of Hospital Clinico San Carlos (Internal Code: 21/128-E) and, when needed, in all involved centers.

DM type II

DM type II was known and diagnosed by medical physicians. Data were collected from the patient's medical records.

Post-COVID-19 syndrome

Patients suffering from post-COVID-19 syndrome describe new-onset symptoms following initial recovery from an acutely confirmed COVID-19 or ongoing from the initial illness. This condition occurs 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms may also fluctuate or relapse over time (11).

Outcomes and follow-up

We described long-term mortality as a primary endpoint. Readmission, reinfection rate, respiratory complications, cardiovascular, neuropsychiatric, respiratory, gastrointestinal, and other symptoms as secondary endpoints were also evaluated. Follow-up for the overall population for mortality was 20 months (mean post-COVID-19; 2.6 ± 4.6).

Statistical analysis

Descriptive and comparative analyses were presented. Continuous variables were shown as mean ± standard deviation if the distribution was normal or median (min–max) if not. Categorical variables were presented as frequency rates and percentages. The Chi-square test was used for categorical variables for group comparisons. Quantitative variables were performed using the Mann–Whitney *U* test for nonparametric variables and the Student's *t*-test for parametric variables, as verified by the Kolmogorov–Smirnov test. We applied a propensity score (PS)-based matching method to control for confounding baseline variables due to the nonrandomized nature of the study and the different participating centers. In a multivariable logistic regression test, hazard ratio (HR) with 95% confidence intervals (95% CI) was calculated for the determination of risk factors for the endpoint. Predictors of mortality were identified by univariate analysis. Predictors with $p < 0.05$ were analyzed by logistic multivariable regression. The multivariable regression test was used to investigate predictors of mortality, adjusting for all significant variables: age; male as sex; obesity; comorbidities such as arterial hypertension, dyslipidemia, DM type II, renal insufficiency, heart disease, cerebrovascular disease, liver disease, and cancer disease; immunosuppression; home oxygen therapy; premedication; symptomatic; clinical parameters such as peripheral oxygen saturation (SpO_2) <92% and reduced blood pressure (systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg); and laboratory parameters. *p*-value of <0.05 was recognized as statistically significant. Statistical analysis was performed with IBM SPSS Statistics version 27.

Results

Baseline characteristics and in-hospital complications

Data from 8,719 consecutive hospitalized patients ($n = 1,578$ with DM; $n = 7,141$ with non-DM) with confirmed COVID-19 were collected. The 1:1 propensity score matching (PSM) according to age and sex resulted in 1,548 matched pairs. The mean age of matched pairs was 72.6 ± 12.7 years old. Even more, the male sex was 63.5% in both groups. Diabetics suffered from more chronic conditions such as arterial hypertension (77.5% vs. 58.5%; $p < 0.0001$), renal insufficiency (13.6% vs. 8.1%; $p < 0.0001$), and liver disease (5.7% vs. 3.4%; $p = 0.002$). In-hospital complications were observed more in diabetics as compared to nondiabetics, for example, respiratory insufficiency (62.1% vs. 56.3%; $p = 0.001$), acute kidney injury (26.6% vs. 19.8%; $p < 0.0001$), and sepsis (15.4% vs. 12.8%, $p = 0.04$). Other baseline characteristics, immunosuppression, home oxygen therapy, premedication, symptomatic, clinical, and laboratory parameters, in-hospital complications, and intervention procedures during hospitalization are presented in Table 1.

Clinical outcomes at long-term follow-up

Mean follow-up (2.6 ± 4.6 months) data were available for 412 diabetics and 443 nondiabetics. The readmission rate due to any cause was similar in diabetics and nondiabetics, respectively (19.7% vs. 18.3%; $p = 0.61$). The reinfection rate with COVID-19 was also comparable in patients with DM than those without DM (2.9% vs. 2.3%; $p = 0.55$). Additionally, diabetics were vaccinated more than nondiabetics at follow-up with the same time to vaccination (11.9 ± 3.1 months in diabetics vs. 12.2 ± 2.9 months in nondiabetics) (57.3% vs. 51.7%; $p = 0.10$). At follow-up, cardiovascular symptoms such as dyspnea and an increase in resting heart rate after discharge occurred less frequently in patients suffering from DM (13.2% vs. 16.4%; $p = 0.01$) than those without DM (2.8% vs. 5.6%; $p = 0.05$), respectively. In addition, the mortality rate at the 20-month follow-up was significantly higher in DM than in non-DM patients (33.9% vs. 29.1%; $p = 0.005$). Cardiovascular, neuropsychiatric, respiratory, gastrointestinal, and other symptoms are presented in Table 2.

TABLE 1 Patients with diabetes mellitus type II as compared to patients without DM II, baseline characteristics, laboratory and radiographic findings, complications, and clinical outcomes.

Characteristic	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Age (mean ± SD (years))	72.6 ± 12.7	72.6 ± 12.7	1.00
Male as sex (no. (%))	983 (63.5)	983 (63.5)	1.00
Chronic conditions (no. (%))			
Arterial hypertension	1,200 (77.5)	906 (58.5)	**<0.0001**
Dyslipidemia	927 (59.9)	551 (35.6)	**<0.0001**
Obesity	486 (31.4)	221 (14.3)	**<0.0001**
Current smoking	86 (6.2)	83 (5.9)	0.73
Renal insufficiency[a]	211 (13.6)	126 (8.1)	**<0.0001**
Lung disease	362 (30.1)	329 (28)	0.26
Cardiac disease	538 (34.8)	414 (26.7)	**<0.0001**
Cerebrovascular disease	192 (12.4)	164 (10.6)	0.12
Connective tissue disease	48 (3.1)	43 (2.8)	0.60
Liver disease	88 (5.7)	52 (3.4)	**0.002**
Cancer disease	291 (18.8)	237 (15.3)	**0.009**
Immunosuppression[b]	134 (8.7)	112 (7.2)	0.14
Home oxygen therapy	74 (4.8)	71 (4.6)	0.80
Premedication (no. (%))			
ASA	453 (29.3)	263 (17)	**<0.0001**
Antiplatelet drug	119 (7.7)	75 (4.8)	**0.001**
Oral anticoagulation	251 (16.2)	220 (14.2)	0.12
Beta-blockers	420 (27.1)	287 (18.5)	**<0.0001**
ACEI/ARB	863 (55.8)	638 (41.2)	**<0.0001**
Symptomatic (no. (%))			
Asymptomatic	81 (5.2)	105 (6.8)	0.07
Dyspnea	961 (62.9)	911 (59.5)	**0.05**
Tachypnea > 22 breaths/min	485 (31.4)	455 (29.4)	0.24
Hemoptysis	26 (1.7)	32 (2.1)	0.42
Fatigue	727 (47)	718 (46.4)	0.75
Anosmia/hyposmia	55 (3.6)	67 (4.3)	0.27
Dysgeusia	66 (4.3)	73 (4.7)	0.54
Sore throat	117 (7.6)	159 (10.3)	**0.01**
Fever	1,102 (71.3)	1,150 (74.4)	0.06
Cough	950 (61.5)	944 (61.1)	0.83
Vomiting	107 (6.9)	95 (6.1)	0.38
Diarrhea	268 (17.3)	234 (15.1)	0.10
Erythromelalgia	369 (23.9)	443 (28.7)	**0.003**
Clinical parameters (no. (%))			
Peripheral oxygen saturation < 92%	690 (44.6)	604 (39.1)	**0.002**

(Continued)

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TABLE 1 Continued

Characteristic	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Abnormal blood pressure[c]	139 (9.9)	116 (8.3)	0.13
GCS < 15	149 (11.8)	144 (11)	0.62
Laboratory parameters (no. (%) or median (min–max))			
Elevated D-dimer	953 (61.6)	903 (58.4)	0.07
Elevated procalcitonin	302 (19.5)	231 (14.9)	**0.0007**
Elevated CRP	1,382 (89.4)	1,343 (86.9)	**0.03**
Elevated TnI	206 (13.3)	165 (10.7)	**0.02**
Elevated transaminases[d]	505 (32.7)	579 (37.5)	**0.006**
Elevated ferritin	494 (32)	515 (33.3)	0.42
Elevated triglyceride	172 (11.1)	129 (8.3)	**0.009**
Elevated LDH	1,018 (65.9)	1,033 (66.8)	0.59
Creatinine (mg/dl)	1.02 (0.38–11.3)	0.96 (0.12–33.9)	**0.0005**
Leukocytes (10E9/L)	7,000 (550–90,004)	6,440 (440–88,400)	**<0.0001**
Lymphocytes (10E9/L)	960 (12–41,100)	930 (244–77,100)	0.25
Hemoglobin (g/dl)	13 (1–19.3)	14 (4–18)	**<0.0001**
Thrombocytes (10E9/L)	201,000 (13,000–716,000)	190,000 (10,000–980,000)	**<0.0001**
Natrium level (mmol/L)	137 (115–179)	138 (117–180)	**<0.0001**
In-hospital complication			
Respiratory insufficiency	958 (62.1)	867 (56.3)	**0.001**
Heart failure	191 (12.4)	128 (8.3)	**0.0002**
Acute kidney injury	411 (26.6)	305 (19.8)	**<0.0001**
Upper respiratory tract infection	257 (16.7)	240 (15.6)	0.41
Pneumonia	1,344 (89.4)	1,336 (88.4)	0.41
SIRS	389 (25.2)	355 (23)	0.16
Sepsis	238 (15.4)	197 (12.8)	**0.04**
Any relevant bleeding[e]	65 (4.2)	46 (3)	0.07
Embolic event	49 (3.2)	47 (3.1)	0.84
Oxygen therapy			
O_2 at the admission	1,238 (80.2)	1,157 (75.1)	**0.0007**
High-flow nasal cannula	347 (22.5)	336 (21.8)	0.65
Noninvasive mechanical ventilation	250 (16.2)	237 (15.4)	0.54
Invasive mechanical ventilation	163 (10.6)	123 (8)	**0.01**
Another medication or intervention procedures during the admission			
Prone position	196 (12.7)	169 (11)	0.14
ECMO	119 (7.7)	82 (5.3)	**0.007**
Use of glucocorticoids	546 (35.4)	526 (34.1)	0.47
Use of hydroxychloroquine	1,173 (76)	1,180 (76.6)	0.69
Use of antiviral drugs[f]	714 (46.2)	812 (53)	**0.0003**
Use of interferon	180 (11.7)	233 (15.1)	**0.005**

(Continued)

TABLE 1 Continued

Characteristic	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Use of tocilizumab	131 (8.5)	128 (8.3)	0.85
Use of antibiotics	1,181 (76.5)	1,113 (72.2)	**0.007**
ACEI/ARB[g]	476 (30.9)	354 (23)	**<0.0001**
Anticoagulation	856 (81.7)	791 (75.8)	**0.001**
Discharge			
ACEI/ARB	82 (30.8)	71 (24.7)	0.11
Antiplatelet drug	226 (14.7)	147 (9.6)	**<0.0001**
Anticoagulation	413 (26.8)	365 (23.7)	**0.05**

ASA, acetylsalicylic acid; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; CRP, C-reactive protein; GCS, Glasgow coma scale; ECMO, extracorporeal membrane oxygenation; SIRS, systemic inflammatory response syndrome; TnI, high-sensitivity troponin I (cardiac injury; troponin > 99th percentile upper reference limit).
[a]CrCL < 30.
[b]Immunosuppressive therapy for psoriatic arthritis, lung transplantation, kidney transplantation, or systemic lupus erythematosus; oncological diseases such as mamma-ca, prostate-ca, myelodysplastic syndrome, or gammopathy; glucocorticoid therapy caused by COPD; dialysis; HIV; or hepatitis.
[c]Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg.
[d]ALAT and ASAT.
[e]Rectorrhagia, hematuria, epistaxis, and popliteal aneurysm bleeding with relevant decreased hemoglobin > 2 mg/l.
[f]Lopinavir or/and ritonavir.
[g]Premedication with ACEI/ARB is not stopped.
*Statistical significance level is set at 0.05 and value of statistical significance is emphasized in bold.

TABLE 2 Follow-up in patients suffering from DM type II as compared to those without DM.

	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Follow-up (mean ± SD)			
Follow-up time (months (PCS))	2.6 ± 4.6	2.8 ± 4.9	0.77
Duration to recovery (months)	2.2 ± 4.6	2.4 ± 4.9	0.51
Duration to readmission (months)	2.5 ± 4.5	2.6 ± 4.6	0.95
Number of patients (*n*)	412	443	–
Readmission	81 (19.7)	81 (18.3)	0.61
Vaccination	236 (57.3)	229 (51.7)	0.10
Time to vaccination (months)	11.9 ± 3.1	12.2 ± 2.9	0.74
Reinfection with COVID-19	12 (2.9)	10 (2.3)	0.55
Clinical event after discharge	171 (43.1)	181 (42)	0.75
Cardiovascular symptoms			
Fatigue	114 (28.7)	125 (29)	0.93
Dyspnea	204 (13.2)	254 (16.4)	**0.01**
Dizziness	34 (8.6)	35 (8.1)	0.82
Chest pain	28 (7.1)	28 (6.5)	0.75
Acute coronary syndrome	3 (0.8)	4 (0.9)	1.00
Palpitation	24 (6.1)	37 (8.6)	0.16
Increase in resting heart rate	11 (2.8)	24 (5.6)	**0.05**
Syncope	2 (0.5)	8 (1.9)	0.11
Arrhythmias	27 (6.8)	22 (5.1)	0.30
Atrial fibrillation	21 (5.3)	26 (6)	0.65

(Continued)

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TABLE 2 Continued

	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Perimyocarditis	1 (0.3)	2 (0.5)	1.00
Limb edema	13 (3.3)	18 (4.2)	0.50
New hypertension	2 (0.5)	7 (1.6)	0.18
New left ventricular dysfunction	5 (1.3)	7 (1.6)	0.66
Relevant bleeding	5 (1.3)	5 (1.2)	0.90
Neuropsychiatric symptoms			
Headache	11 (2.8)	21 (4.9)	0.12
Migraine	5 (1.3)	11 (2.6)	0.18
Ageusia	17 (4.3)	19 (4.4)	0.93
Anosmia	12 (3)	18 (4.2)	0.38
Attention disorder	16 (4)	25 (5.8)	0.24
Memory loss	31 (7.8)	34 (7.9)	0.97
Cognitive disorder	18 (4.5)	20 (4.6)	0.94
Anxiety	34 (8.6)	54 (12.5)	0.06
Depression	26 (6.6)	35 (8.1)	0.39
Tinnitus or hearing loss	9 (2.3)	14 (3.3)	0.39
Sleeping disorder	27 (6.8)	36 (8.4)	0.40
Mood disorder	22 (5.5)	31 (7.2)	0.33
Paranoia	16 (4)	5 (1.2)	**0.009**
Respiratory symptoms			
Cough	33 (8.3)	42 (9.7)	0.47
Reduce pulmonary diffusing capacity	28 (7.1)	44 (10.2)	0.11
Polypnea	15 (3.8)	19 (4.4)	0.65
Sleep apnea	13 (3.3)	9 (2.1)	0.29
Gastrointestinal symptoms			
Tongue involvement	1 (0.3)	7 (1.6)	0.07
Digestive disorder	20 (5)	17 (3.9)	0.45
Nausea/vomiting	10 (2.5)	8 (1.9)	0.51
Other symptoms			
Intermittent fever	8 (2)	10 (2.3)	0.76
Chills	6 (1.5)	8 (1.9)	0.70
Hair loss	20 (5)	18 (4.2)	0.55
Joint pain	19 (4.8)	25 (5.8)	0.52
Myalgia	26 (6.6)	32 (7.4)	0.62
Sweat	5 (1.3)	4 (0.9)	0.74
Weight loss	24 (6.1)	23 (5.3)	0.66
Cutaneous involvement	6 (1.5)	13 (3)	0.15
New diabetes	–	4 (0.9)	–
New renal insufficiency	19 (4.8)	11 (2.6)	0.09

(Continued)

TABLE 2 Continued

	Diabetics (*N* = 1,548)	Nondiabetics (*N* = 1,548)	*p*-value*
Pain	12 (3)	8 (1.9)	0.28
Red eyes	4 (1)	6 (1.4)	0.76
Flushing	4 (1)	2 (0.5)	0.43
Incident neoplasia	2 (0.5)	6 (1.4)	0.29
Management after discharge			
Home oxygen therapy	43 (10.8)	37 (8.6)	0.27
ASA	99 (24.9)	58 (13.5)	**<0.0001**
Antiplatelet drug	34 (8.6)	23 (5.3)	0.07
Anticoagulation	69 (17.4)	54 (12.5)	**0.05**
ACEI/ARB	140 (35.3)	113 (26.2)	**0.005**
Beta-blockers	75 (18.9)	69 (16)	0.27
Beta agonist inhalation therapy	34 (8.6)	46 (10.7)	0.31
Vitamin supplementation	72 (18.1)	80 (18.6)	0.88
Antidepressant	47 (11.8)	64 (14.9)	0.20
Statin	151 (38)	103 (23.9)	**<0.0001**
Diagnostic test after discharge			
Elevated di-dimer	137 (34.6)	151 (35.2)	0.86
Elevated CRP	167 (42.2)	183 (42.7)	0.89
Elevated procalcitonin	45 (11.4)	34 (7.9)	0.09
Elevated TnI	18 (4.6)	16 (3.7)	0.56
Elevated NT-proBNP	23 (5.8)	29 (6.8)	0.57
Elevated transaminases[a]	92 (23.2)	100 (23.3)	0.98
Abnormal spirometry	21 (18.8)	17 (13)	0.24
Any chest X-ray abnormality	99 (39.4)	103 (38.9)	0.99
Any CT abnormality	37 (35.6)	48 (35.3)	0.60
In-hospital mortality	492 (31.8)	426 (27.5)	**0.009**
Long-term mortality	524 (33.9)	451 (29.1)	**0.005**

PCS, post-COVID-19 syndrome; ASA, acetylsalicylic acid; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; CRP, C-reactive protein; TnI, high-sensitivity troponin I cardiac injury; troponin > 99th percentile upper reference limit. [a]ALAT and ASAT.
*Statistical significance level is set at 0.05 and value of statistical significance is emphasized in bold.
Summarized, - means not available.

PSM and predictors of mortality

The mortality rate at long-term follow-up was significantly higher in patients with DM than those without, in the overall cohort and in the matched cohort, respectively ($p < 0.0001$ and $p = 0.005$). The Kaplan–Meier curve with landmark analysis is displayed in Figure 1. In the multivariable analysis for mortality, age, and male sex were determined as predictors for mortality, respectively (HR: 2.34; $p < 0.0001$) (HRK 1.23; $p = 0.008$). Other predictors are performed in Table 3. Clinical outcomes before PSM are presented in the Supplementary Appendix.

Discussion

This study presents characteristics of PCS in patients suffering from DM as compared to those without DM. The main findings of this study are as follows: (1) readmission rate for any cause was similar in diabetics than nondiabetics at follow-up; (2) reinfection rate with COVID-19 was similar in both groups; (3) symptoms such as dyspnea and an increase of resting heart rate occurred less in diabetics as compared to nondiabetics; (4) The incidence of newly diagnosed arterial hypertension was less in diabetics than nondiabetics without statistical significance; (5) respiratory

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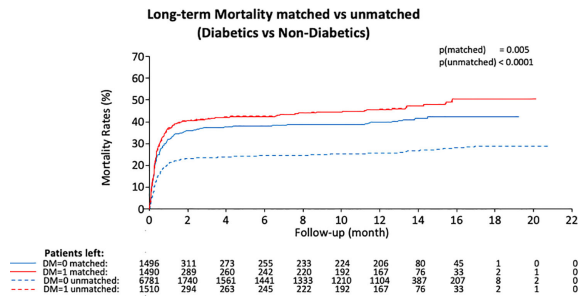

FIGURE 1
Kaplan–Meier curve for long-term mortality divided by diabetics vs. nondiabetics in the overall population and matched cohort. In both comparisons, a worse outcome in diabetics was detected.

complications were revealed in diabetics and nondiabetics; and (5) long-term mortality was higher in patients suffering from DM as compared to those without DM.

Recently, it has been reported that the progression of type II DM is associated with increased insulin resistance accompanied by chronic inflammation and endothelial and ß-cell dysfunction (12). On the other hand, the inflammatory response in infected patients with SARS-CoV-2 may worsen insulin resistance and endothelial dysfunction (13). The existence of both diseases may further enhance the inflammation and decrease interferon levels, neutrophil chemotaxis, and T lymphocyte-mediated immune response with impairment of cytokine production (14–16). That is associated with a severe course of COVID-19 in DM patients. Furthermore, ACE2 expression increases insulin resistance. This receptor and dipeptidyl peptidase 4 (DPP4), which may be a factor in the severity of COVID-19 infection, are present in several physiological processes and are modulated by hyperglycemia and pharmacological therapies that are common in DM patients (17). In addition, chronic hyperglycemia leads to chronic vascular and kidney disease. Other comorbidities, such as obesity and hypertension, are present in concurrent DM. These diabetes-related comorbidities may negatively impact outcomes in DM patients with COVID-19 (18, 19).

DM as a risk factor for post-COVID-19 syndrome

Our DM cohort had more comorbidities such as arterial hypertension, renal insufficiency, liver disease, and cardiac disease than patients without DM. Furthermore, respiratory insufficiency requiring oxygen therapy and invasive mechanical ventilation (MV) was observed more in diabetics as compared to nondiabetics. During hospitalizations, sepsis and acute kidney injury occurred more often in diabetics than nondiabetics. A prospective study showed that the persistence of symptoms was associated with the severity of the disease at the beginning and that the intensive care unit (ICU) admission was an independent risk factor for PCS (20). In addition, the need for MV was determined as a predictor for the development of PCS (21). However, it has been reported that 60% of low-risk patients for mortality with COVID-19 suffered from severe PCS (22). In patients with DM, optimizing hyperglycemia therapy improve metabolic function which may be beneficial for the long-term management of patients with PCS (23). In this study, PCS was slightly comparable despite the different comorbidities and in-hospital complications in both groups.

Cardiovascular symptoms

In our study, dyspnea and an increase in resting heart rate occurred more significantly in nondiabetics as compared to diabetics. Additionally, newly diagnosed arterial hypertension was also revealed slightly more in nondiabetics than diabetics. Regarding that, the persistence of cardiovascular symptoms was recently reported (24). In one of the studies from Wuhan, Huang et al. showed that patients infected with SARS-CoV-2 suffered from acute cardiac injury (25). Subclinical myocarditis with an increased risk of arrhythmias may play a role in PCS (26). Data about the comparison between diabetics and nondiabetics are limited.

Neuropsychiatric symptoms

This study presented neuropsychiatric symptoms generally more common in nondiabetics as compared to diabetics without statistical significance, for example, headache, sleeping disorder, and anxiety. However, paranoia was observed significantly more in diabetics than nondiabetics at a 3-month follow-up. Studies reported that headache and other neuropsychiatric symptoms occurred after 3 months in patients infected with SARS-CoV-2 (27, 28). Guedj et al. reported that more areas in the brain showed hypometabolism in patients with PCS as compared to healthy subjects (29). Controlled, randomized studies are needed to investigate the neuropsychiatric symptoms in patients with DM as compared to those without DM.

Respiratory symptoms

Renal insufficiency and cardiac disease were observed more in patients with DM than non-DM, while the rate of lung diseases was similar in matched pairs. At follow-up, our data presented a similar rate of sleep apnea in diabetics and nondiabetics. Furthermore, computer tomography (CT) and chest X-ray abnormalities were revealed in both groups, but dyspnea occurred significantly more in nondiabetics as compared to diabetics at follow-up. In one retrospective study with 77 days of follow-up, spirometry (9.3%) and chest radiology (19%) abnormalities were detected in 277 patients, of whom 51% had PCS (30). In 22 patients after COVID-19-associated acute respiratory distress syndrome (ARDS), signs of lung fibrosis were detected in 55% of patients at 3-month follow-up (31). In patients with critical COVID-19, 9.5% of patients needed home oxygen therapy after discharge at a 1-year follow-up (32). Furthermore, DM was identified as a risk factor for the requirement of oxygen therapy in patients suffering from COVID-19 (33). In our multivariable analysis, DM was not identified as a predictor for mortality.

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TABLE 3 Predictors of mortality, multivariable analysis.

Variable	Univariable analysis		Multivariable analysis	
	HR	*p*-value	HR	*p*-value
Patient demographics				
Age ≥70	2.90	**<0.0001**	2.34	**<0.0001**
Male	1.19	**0.01**	1.23	**0.008**
Chronic conditions				
Dyslipidemia	1.12	0.07		
Diabetes mellitus	1.18	**0.01**		
Obesity	1.01	0.88		
Renal insufficiency	1.86	**<0.0001**	1.33	**0.003**
Cancer disease	1.46	**<0.0001**		
Immunosuppression	1.41	**0.0009**	1.40	**0.003**
Premedication				
ASA	1.38	**<0.0001**		
Oral anticoagulation	1.66	**<0.0001**		
Clinical parameters				
SpO_2 < 92%[a]	3.14	**<0.0001**	2.13	**<0.0001**
Abnormal blood pressure[b]	2.09	**<0.0001**	1.36	**0.002**
GCS < 15	2.67	**<0.0001**	1.50	**<0.0001**
Clinical presentation				
Dyspnea	1.48	**<0.0001**		
Tachypnea > 22 breaths/min	2.17	**<0.0001**	1.41	**<0.0001**
Dysgeusia	0.32	**<0.0001**	0.40	**0.001**
Sore throat	0.79	0.07		
Cough	0.77	**<0.0001**	0.84	**0.02**
Erythromelalgia	0.73	**<0.0001**		
Laboratory parameters				
Elevated procalcitonin	1.89	**<0.0001**	1.53	**<0.0001**
Elevated CRP	1.60	**<0.0001**		
Elevated LDH	1.50	**<0.0001**	1.20	**0.04**

HR, hazard ratio; ASA, acetylsalicylic acid; SpO_2, peripheral oxygen saturation; GCS, Glasgow coma scale.
[a]SpO_2 < 92% at admission.
[b]Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg.
Statistical significance level is set at 0.05 and value of statistical significance is emphasized in bold.

This study has some limitations. It has a retrospective character; not all laboratory tests were done on all patients. Furthermore, data on hemoglobin A1c (HbA1c), antihyperglycemic treatment including metformin and DPP-4 inhibitors, and statin therapy at baseline are missing. A strength of our study is the sample size of patients with COVID-19 and concomitant DM type II at 55 international centers. The results are therefore real-world evidence.

To summarize, PCS was observed in diabetics and nondiabetics. However, the mortality rate was higher in diabetics as compared to nondiabetics. DM was not determined as a risk factor for mortality at follow-up.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was executed in compliance with the Declaration of Helsinki regarding in human subjects and the study was approved by the center Ethics Committee of Hospital Clinico San Carlos (Internal Code: 21/128-E) and, when needed, in all involved centers. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MA, IG, IE-B, and IA made substantial contributions to the study's concept and design. All authors obtained ethical approval. Data were collected by MA, IG, MV-L, SR, RR, EA-R, AU, GF, VB-M, FS, MP, AM, JS-C, AG, FM, JL-P, EM, OC, CP, AM, LV, DC, AF-O, MA, and CW analyzed all the data. CW supported the descriptive statistics. IJNG and IA approved the statistical analysis. MA, IG, IE-B, and IA prepared the manuscript. All authors contributed to the article and approved the submission version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1167087/full#supplementary-material

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