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ORIGINAL RESEARCH

What Impact Does Glycemic Control Have on the Final Outcome of Diabetic Patients with Severe COVID-19?

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Abstract

Background: Diabetes represents one of the most frequently reported comorbidities in patients with COVID-19 disease; and is a risk factor for disease progression, and death.

Aim: Assessing the impact of glycemic control on the progression of Covid-19 disease.

Materials and methods: This is a mixed cohort study, from November 2020 to November 2021, with 369 diabetic patients hospitalized for covid-19, at the Duc De Tovar hospital in Tangier. With a follow-up at D7, D14, D21, D28, and the thirtieth day after hospital discharge.

Results: We objectified a male predominance (61.5%), the average age being 60-years-old (+/-11.25; (18-85)). 126 diabetic patients were admitted to the reanimation unit (34.1%), and 243 to the intensive care unit (65.9%).190 patients had satisfactory glycemic control (51.5%), and glycemic targets were not reached in 179 patients (48.5%).

Unfavorable progression was defined by in-hospital mortality, which was our primary judgment criterion. Thus, 162 patients died in the 2 admission units (43.9%), including 67 patients in the intensive care unit (41%) and 95 patients in the reanimation unit (59%). The unfavorable progression of the Covid-19 disease was not significantly related to the glycemic control during hospitalization, but significantly related to the respiratory distress syndrome (p = 0.030), to the transfer to reanimation unit (p = 0.004), to the invasive ventilation (p = 0.026), after multivariate analysis.

Conclusion: According to the results of our study, glycemic control plays a modifying role on the effect of other factors aggravating the progression of Covid-19.

Keywords

COVID-19, Diabetes, Glycemic control, Death

Introduction

Identified in China (Wuhan), in December 2019, the new Coronavirus was responsible for unexplained severe pneumonia, and declared as a pandemic by the World Health Organization in March 2020 [1]. During the pandemic of COVID-19, the major challenge was the difficulty to ensure continuous care, and the risks encountered in case of chronic diseases. Among these, diabetes which is one of the most frequently reported comorbidities in patients with COVID-19, with a prevalence of 10.6% in Morocco, according to the national survey of 2019, this prevalence increases with age from 4% to 23.2% respectively between the age groups of 18-29 years and 60-69 years [2].

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Diabetes and hyperglycemia have emerged as risk factors for disease worsening, intensive care unit (ICU) admissions and death in patients with COVID-19 [3].

This study aims to evaluate the impact of glycemic control on the progression of COVID-19 disease.

Materials and Methods

Type of study

This is a mixed retrospective and prospective cohort study, from November 2020 to November 2021, with a follow-up at admission, at D7, D14, D21, and D28, of 369 diabetic patients hospitalized for covid-19, the Duc De Tovar hospital of Tangier, within two units (intensive care unit, and reanimation unit), and a follow-up of the progression until the thirtieth day after hospital discharge.

Study population

Inclusion criteria: All types of diabetes known or discovered during hospitalization.

Exclusion criteria: Patients who refuse to participate in the study.

Data collection

Data are collected using a CRF (Case Report Form) which has been developed using the International Severe Acute Respiratory and Emerging Infection (USARIC) modified case report form, established by the World Health Organization (WHO) for standardization of collected data, which will allow comparability with other populations.

This CRF consists of four modules:

1. Module 1 to be completed on the first day of hospitalization, containing the anamnesis and sociodemographic data, signs related to Covid-19 and their date of appearance, medications taken prior to admission, comorbidities associated with diabetes-related medical history, admission unit, clinical and paraclinical parameters on admission (results of the RT-PCR (reverse transcription-polymerase chain reaction), rapid antigen test, biological tests, chest CT and electrocardiogram), supportive care (oxygen therapy), and treatment started (hydroxychloroquine, antibiotic therapy, corticosteroid therapy, anticoagulation, insulin therapy, vitamin C, zinc, vitamin D, and others).
2. Module 2 for follow-up, to be completed at D7, D14, D21, and D28, containing clinical, biological, supportive care and treatment assessment, occurrence of acute metabolic complications (diabetic ketoacidosis, hyperosmolar coma, severe hypoglycemia), as well as other complications (acute respiratory distress syndrome, pulmonary embolism, acute renal failure, and others), and the patient's status at the end of the week.
3. Module 3 regarding the patient's outcome, either discharge with or without supportive care, or death.
4. Module 4 concerning the progression of patients at D15 and D30 after hospital discharge.

Definition of variables

The diagnosis of COVID-19 disease was based on WHO guidelines by identification of SARS-COV-2 viral RNA using the PCR technique, or by rapid antigenic tests, or on radiological data on chest CT.

The criteria for admission to the intensive care unit and reanimation unit were based on the criteria set by the Ministry of Health:

- Admission to the Intensive Care Unit: oxygen saturation (SpO_2) < 92% without signs of severe respiratory failure; or a COVID positive patient requiring close monitoring (decompensated comorbidity...).

- Admission to the Reanimation Unit: Need for invasive or non-invasive ventilation (SpO_2 < 90% with signs of severe respiratory failure, SpO_2 < 92% on 8 l/min of O_2 or on a high concentration mask for more than one hour; or presence of other acute life-threatening failures.

The diagnosis of diabetes: Either self-reported as a medical history, or newly diagnosed by a fasting blood glucose level higher than or equal to 1.26 g/l; or a blood glucose level higher than 2 g/l at any time of the day during the hospital stay; or by a glycated hemoglobin (HBA1c) higher than or equal to 6.5%.

Hyperglycemia was defined as a blood glucose level of 1.80 g/L;

A blood glucose level higher than or equal to 2.50 g/L defines severe hyperglycemia.

Hypoglycemia was defined as a blood glucose level below 0.70 g/l.

All diabetic patients hospitalized for covid-19, received insulin therapy, with discontinuation of ADO.

Different insulin regimens were initiated:

- Basal insulin regimen with one to three boluses of rapid insulin;
- Basal insulin regimen with corrective boluses of rapid insulin depending on capillary glucose;
- Basal insulin regimen only.

The routine protocol for blood glucose monitoring during hospitalization was set at seven measurements per day (fasting, before meals, two hours after meals and at bedtime). For patients who did not eat properly, or who were intubated, capillary blood glucose monitoring every four hours was implemented.

The glycemic objectives are set at a capillary glycemia between 1.40 g/l and 1.80 g/l. These glycemic objectives are adapted for certain patients in critical situations (elderly subjects, severe renal insufficiency, cardiopaths) for whom a capillary glycemia between 1.80 g/l and 2 g/l is tolerable.

The assessment of glycemic control during hospitalization is defined according to the capillary blood glucose values, so we divided the diabetic hospitalized patients into two groups:

- A group of patients in whom glycemic control was obtained, with a blood glucose level between 1.40 g/l and 1.80 g/l.
- A group of patients in whom glycemic control has not been obtained, with blood glucose levels above 1.80 g/L

The primary judgment criterion in our study is defined by in-hospital death.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics software-version 21. Quantitative variables were described as averages ± standard deviations and qualitative variables were described as proportions/numbers. The graphs were created from a descriptive analysis of the IBM SPSS Statistics software-version 21 and the Excel Graph Generator.

Univariate analysis: The comparison of percentages was performed by cross-tabulation using the Chi-square test or Fisher's exact test. The comparison of averages was made using the one-factor ANOVA method. The significance level adopted was 0.05.

Multivariate analysis: Binary logistic regression models were created for the multivariate analysis. They were obtained using the factor(s) identified as significant in the univariate analysis, the significance level adopted being 0.2.

Ethical and regulatory aspects

Respect of ethical aspects: (anonymity; informed consent of the patient; voluntary participation), the approval of the ethics committee was required for this study by the University Hospital Ethics Committee of Fez, on February 11, 2021.

Results

Results of the descriptive analysis

Clinical characteristics of diabetic patients hospitalized for covid-19: Clinical characteristics were collected from a total of 369 diabetic patients, 126 of whom were admitted to the reanimation unit (34.1%), and 243 to the intensive care unit (65.9%).

Among the diabetic patients hospitalized, we have identified 142 women (38.5%) and 227 men (61.5%).

The average age was 60 years (+/-11.25; (18-85)), and 64 years (+/-12.67; (28-95)), respectively in the patients admitted to the reanimation unit and the intensive care unit.

Among the diabetic patients admitted to the hospital, we have identified 68 overweight patients (39.1%), and 62 obese patients (35.6%).

The average time from the date of first symptom to the date of admission was 8.59 days (+/- 5.12), with no significant difference between the two admission sites.

All our diabetic patients admitted to hospital were symptomatic, with the most frequent symptoms represented by dyspnea (82.9%), fever (79.6%), cough (78.9%), headache (51.7%), and asthenia (42.7%).

The main comorbidities in our patients were arterial hypertension in 43.6% of cases, chronic heart disease in 12.5% of cases, and chronic renal failure in 6.4% of cases.

Among the hospitalized diabetic patients, 273 were known to be diabetic (74%); and 96 patients presented an inaugural diabetes (26%). 269 of the 273 known diabetic patients were suffering from type 2 diabetes (98.5%).

The progression of diabetes for more than 10 years was reported in 120 patients (32.7%). Among the 273 known diabetic patients, 175 patients were on oral antidiabetics (64%); 78 patients were on insulin therapy (29%); and 20 patients were on a combination of insulin and oral antidiabetics (7%).

Among the known diabetic patients, 138 patients had a previous glycemic imbalance (72.2%). The extent of pulmonary lesions on chest CT was severe in 130 patients (35.9%), and critical in 103 patients (28.5%).

At admission, 298 patients had an oxygen saturation of less than 90% (81%).

Therapeutic characteristics of diabetic patients hospitalized for covid-19: At admission, 353 patients required oxygen therapy (96.7%), with an oxygen flow rate higher than 15 liters/min in 134 patients (38%). Invasive ventilation was necessary in 64 patients (17.3% of cases).

Antibiotic therapy during hospitalization was given to 78% of our patients, synthetic glucocorticoids to 79.2% of the patients, and curative anticoagulation to 77% of the patients.

Among the hospitalized diabetic patients, 323 were placed on insulin therapy, of which 298 were on a basal bolus regimen (80.76%), and 46 patients were on glycemic monitoring alone (12.5%).

Complications during hospitalization: The main complications during hospitalization consisted of superinfection in 48% of cases, acute respiratory distress syndrome (ARDS) in 27.7% of cases, pulmonary embolism in 12.2% of cases, and ketoacidosis decompensation in 9.5% of cases.

Progression of diabetic patients hospitalized for covid-19:

i. **Adverse progression:** Defined by in-hospital mortality, which is our primary judgment criterion. During hospitalization, 162 patients died in the 2 admission units (43.9%), including 67 patients in the intensive care unit (41%), and 95 patients in the reanimation unit (59%).

ii. **Patient outcome after hospital discharge:** During the follow-up of 207 patients discharged alive from the hospital, it was found that 13 patients died within 30 days after discharge (6%), and 43 patients were lost to follow-up (21%).

iii. **Glycemic control:** Based on capillary blood glucose values, our diabetic patients were divided into two groups: A group in which glycemic control was considered satisfactory, consisting of 190 patients (51.5%), and another group in which glycemic targets were not reached, represented by 179 patients (48.5%).

Characteristics of patients according to glycemic control groups (Table 1): Patients with satisfactory glycemic control had an average admission blood

Table 1: Characteristics of patients in the satisfactory control and non-achieved control groups.

	Satisfactory control (n = 190; 51.5%)	**Non-achieved control (n = 179; 48.5%)**
Parameters		
Admission unit: n (%)		
Intensive care	128 (67.4)	115 (64.2)
Reanimation	62 (32.6)	64 (35.8)
Clinical characteristics on admission n/N (%)		
Male gender n (%)	101 (53.2)	126 (70.4)
Female gender n (%)	89 (46.8)	53 (29.6)
Fever	144/187 (77.0)	145/176 (82.4)
Cough	149/184 (81.0)	135/176 (76.7)
Dyspnea	155/185 (83.8)	145/177 (81.9)
Asthenia	78/185 (42.2)	76/176 (43.2)
Headache	101/185 (54.6)	85/175 (48.6)
Vomiting	54/182 (29.7)	39/176 (22.2)
Diarrhea	42/181 (23.2)	37/176 (21.0)
Associated Comorbidities n/N (%)		
Chronic heart disease	26/182 (14.3)	19/177 (10.7)
High blood pressure	80/182 (44.0)	77/178 (43.3)
Chronic kidney failure	15/183 (8.2)	8/178 (4.5)
Dyslipidemia	8/178 (4.5)	12/175 (6.9)
Neurological disorder	1/185 (0.5)	4/177 (2.3)
Smoking	9/171 (5.3)	9/ 154 (5.8)
History of diabetes (%)		
Duration of diabetes :		
< 5 years	32 (16.8)	24 (15.7)
Between 5-10 years	36 (18.9)	51 (28.4)
> 10 years	48 (25.2)	72 (40.2)
inaugural diabetes	60 (31.6)	36 (20.1)
Previous glycemic balance:		
good n/N	29/86 (33.7)	24/105 (22.9)
Unbalance n/N (%)	43/86 (50.0)	48/105 (45.7)
Majeur imbalance n/N (%)	14/86 (16.3)	33/105 (31.4)
Biological Parameters on admission		
Blood glucose. median (g/l)	1.92 (0.64-4.19)	2.73 (0.32-5.42)

A1c hemoglobin. median (%)	8.02 (4.30-13.30)	9.59 (5.10-14.80)
CRP >= 70 mg/l n/N (%)	113/139 (81.3)	103/132 (78.0)
Therapeutic management n/N (%)		
Oxygenotherapy n (%)	185 (97.3)	168 (93.8)
Antibiotic therapy	90/120 (75.0)	87/107 (81.3)
Corticosteroid therapy	89/119 (74.8)	90/107 (84.1)
Hydroxychloroquin	87/181 (45.8)	97/173 (54.2)
Complications during hospitalization n/N (%)		
ARDS	32/121 (26.4)	32/110 (29.1)
Pulmonary embolism	14.7/190 (14.7)	17/179 (9.5)
Acute kidney failure	9/99 (9.1)	8/96 (8.3)
Hepatic dysfunction	11/96 (11.5)	5/83 (6.0)
Pulmonary surinfection	90/ 190 (47.4)	87/179 (48.6)
DKA	4/104 (3.8)	15/95 (15.8)
Severe hypoglycemia	9/107 (8.4)	3/98 (3.1)

CRP: C-reactive Protein; ARDS: Acute Respiratory Distress Syndrome; DKA: Diabetic Ketoacidosis

Table 2: Factors associated with in-hospital mortality in diabetics hospitalized for Covid-19.

	Intra-hospital death								
	Total			**Satisfactory control**			**Non-achieved control**		
	n	**%**	**p**	**n**	**%**	**p**	**n**	**%**	**p**
Gender	369		0.014	190		0.466	179		0.007
Male		48.9			44.6			52.4	
Female		35.9			39.3			30.2	
Chronic heart disease	359		0.286	182		0.325	177		0.560
No		42.7			39.7			45.6	
Yes		51.1			50			52.6	
Hight blood pressure	360		0.497	182		0.740	178		0.536
No		44.3			41.2			47.5	
Yes		40.8			38.8			42.9	
Dyslipidemia	353		0.469	178		0.022 (Fisher)	175		0.320
No		43.2			42.9			43.6	
Yes		35.0			0.0			58.3	
Asthma	362		0.910	185		0.719 (Fisher)	178		0.627 (Fisher)
No		43.3			40.7			46.0	
Yes		41.7			50			25.0	
Chronic kidney failure	361		0.370	183		0.118	178		0.729 (Fisher)
No		42.6			39.3			45.9	
Yes		52.2			60			37.5	
Type of diabetes	273		NA	130		NA	143		NA
Type 1		0.0			-			0.0	
Type 2		43.1			39.8			46.1	
Gestational		50.0			100			0.0	
Cortico-induced		100			100			-	
Duration of diabetes	309		0.360	156		0.397	153		0.128
Inaugural		45.8			45.0			47.2	
< 5 ans		33.3			29.6			37.5	
5 - 10 ans		45.8			32.3			56.1	
> 10 ans		41.4			44.7			32.7	
Dietary measures	196		0.129	89		0.123	107		0.539

No		43.1			43.3			42.9	
Yes		32.3			27.1			36.9	
Pre-admission oral antidiabetics	233		0.684	105		0.041	128		0.210
No		42.4			51.7			35.1	
Yes		39.5			30.3			47.3	
Pre-admission insulin therapy	226		0.066	101		0.899	125		0.015
No		43.9			36.0			51.3	
Yes		31.0			34.6			28.9	
Previous glycemic control	191		0.321	86		0.593	105		0.448
Good balance		32.1			31.0			33.3	
Imbalance		39.9			36.8			42.0	
Surinfection	369		0.436	190		0.975	179		0.247
No		45.8			42.0			50	
Yes		41.8			42.2			41.4	
SDRA	231		0.000	121		0.000	110		0.000
No		21.6			23.6			19.2	
Yes		73.4			68.8			78.1	
Pulmonary embolism	369		0.573	190		0.458	179		0.913
No		44.4			43.2			45.7	
Yes		40.0			35.7			47.1	
Acute kidney failure	196		0.074	100		0.194 (Fisher)	96		0.479 (Fisher)
No		39.2			39.3			39.1	
Yes		60.0			63.6			55.6	
Severe hypoglycemia	205		0.687	107		1.000 (Fisher)	98		1.000 (Fisher)
No		38.6			37.9			39.4	
Yes		43.8			41.7			50.0	
Diabetic ketosis	198		0.677	104		0.255 (Fisher)	94		0.473 (Fisher)
No		38.5			36.5			40.7	
Yes		43.8			62.5			25.0	
Diabetic ketoacidosis	199		0.274	104		0.71 (Fisher)	95		0.927
No		37.4			36.4			38.8	
Yes		50.0			80.0			40.0	
Hyperglycemia on admission	233		0.436	116		0.192	177		0.799
No		43.9			43.2			45.5	
Yes		38.9			31.0			42.9	
CRP>= 70 mg/l	271		0.054	139		0.922	132		0.008
No		34.5			42.3			27.6	
Yes		49.1			43.4			55.3	
Hydroxychloroquin intake	354		0.066	181		0.068	173		0.380
No		48.8			47.9			50.0	
Yes		39.1			34.5			43.3	
Pre-admission anticoagulants	365		0.001	187		0.099	178		0.004
No		46.7			44.1			49.4	
Yes		21.7			26.9			15.0	
Extent of CT lesions on admission	362		0.000	187		0.000	175		0.000
< 25 %		3.1			5.9			0.0	

25-50%		33.0			29.6			37 .2	
50-75%		41.5			40.0			43.1	
> 75%		68.0			66.7			69.2	
Oxygen saturation on admission	347		0.000	177		0.003	170		0.012
< 90%		49.6			50.0			49.3	
90-92%		29.6			14.3			46.2	
92-94%		25.0			16.7			30.0	
> 94%		10.7			17.6			0.0	
Transfer to reanimation	369		0.000	190		0.000	179		0.000
No		22.1			23.1			21.0	
Yes		75.0			72.6			77.2	
Invasive ventilation	369		0.000	190		0.000	179		0.000
No		31.6			31.6			31.6	
Yes		92.0			93.8			90.7	
Glycemic control during hospitalization	369		0.474						
Not achieved		45.8							
Achieved		42.1							

Table 3: Factors associated with in-hospital mortality in diabetics hospitalized for covid19. (Average (± standard deviations)).

	Total			**Satisfactory control**			**Non-achieved control**		
	Deaths	**Survivor**	**p**	**Deaths**	**Survivor**	**p**	**Deaths**	**Survivor**	**p**
Age	64.10 ± 12.55	61.44 ± 11.95	0.041	63.37 ± 13.17	62.75 ± 11.29	0.733	64.82 ± 11.93	59.92 ± 12.59	0.009
Interval (**Date of onset of symptoms - Date of admission**)	8.38 ± 5.195	8.87 ± 5.03	0.371	8.66 ± 5.43	9.82 ± 5.62	0.163	8.11 ± 4.967	7.82 ± 4.058	0.684

glucose level of 1.92 g/l ((+/-0.80) versus 2.73 g/l (+/-1.09)); with an average admission HBA1c of 8.02% ((+/-1.84) versus 9.59% (+/-2.19)).

The need for intensive treatment was less pronounced in the group with satisfactory glycemic control, with antibiotic therapy required in 75% of cases (versus 81.3%); corticosteroid therapy in 74.8% of cases (versus 84.1%).

The rate of complications during hospitalization was lower in the group with satisfactory glycemic control, with ARDS in (26% versus 29.1%), superinfection in (47.4% versus 48.6%), and ketoacidosis decompensation in (3.8% versus 15.8%).

A reduction in the rate of transfer to reanimation unit in the group with satisfactory glycemic control was registered in 38.4% (versus 49.7%), with a reduction in the death rate in 45.3% (versus 49.7%). However, there was an increased risk of severe hypoglycemia in this group (8.4% versus 3.1%).

Results of the univariate analysis

In the univariate analysis we studied the factors associated with in-hospital mortality in our diabetic patients hospitalized for COVID-19; the results are reported in Table 2.

We also studied other factors associated with in-hospital mortality, including age and time interval between the first symptom and admission; the results are reported in Table 3.

We also studied in the univariate analysis the factors related to the obtaining of glycemic control during hospitalization; the results are reported in Table 4.

Results of the multivariate analysis

Logistic regression models constructed for the multivariate analysis of adverse progression, using the factor(s) identified as significant in the univariate analysis and forcing the variables dietary measures, respiratory distress syndrome, transfer to reanimation, and invasive ventilation, are reported in Table 5.

Discussion

Our study concerned only diabetic patients hospitalized for a severe form of Covid-19 disease in intensive care unit (ICU) and in reanimation unit; our objective was to study the relation between glycemic control during hospitalization and the adverse

Table 4: Factors related to achieving glycemic control during hospitalization.

	Satisfactory control (%)	Non-achieved control (%)	p	$_b$RR	IC 95%
Gender			0.001		
Male	44.5	55.5		1	
Female	62.7	37.3		0.47	0.31-0.73
Duration of diabetes			0.021		
< 5 ans	52.9	47.1		-	
5-10 ans	43.1	56.9		-	
> 10 ans	42.2	55.8		-	
Inaugural diabetes			0.012		
No	47.6	52.4		1	
Yes	62.5	37.5		0.54	0.33-0.87
Previous glycemic control			0.037		
Good balance	54.7	45.3		-	
Unbalance	47.3	52.7		-	
Major Imbalance	29.8	70.2		-	

$_b$RR: brut Relative Risk; IC à 95%: Confidence interval à 95.

Table 5: Factors associated with in-hospital death in diabetic patients with covid-19: Binary logistic regression.

variables	p	$_a$RR	IC à 95%
Dietary measures	0.050	0.330	0.109-1.002
Respiratory distress syndrome	0.030	4.036	1.143-14.248
Transfer to reanimation	0.004	5.373	1.689-17.089
Invasive ventilation	0.026	6.001	1.240-29.049
Constants	0.000	0.199	

$_a$RR: adjusted Relative Risk; IC à 95%: Confidence interval à 95%.

progression of Covid-19 disease, defined by in-hospital death. Thus, out of 369 hospitalized diabetic patients, 162 patients died in the 2 admission units (43.9%), including 67 patients in the intensive care unit (41%), and 95 patients in the reanimation unit (59%).

The severity of the prognosis of Covid-19 disease noted in the present study is consistent with the results of the French multicenter Coronado study, whose primary judgment criterion consisted of the use of tracheal intubation for mechanical ventilation and/or death within 7 days of admission. Indeed, unlike our study, the Coronado study did not include only patients with a severe form of Covid-19, and it combined the criterion of tracheal intubation with in-hospital death, thus the primary judgment criterion in the Coronado study occurred in 29.0% of the participants, with a tracheal intubation rate of 20.3%, and a mortality rate of 10.6% as of the seventh day after admission [4].

Early observational data, published by Asian teams at the beginning of the pandemic, quickly identified diabetes as a poor prognostic factor in COVID-19 [5,6]. Although very preliminary, this finding was consistent with data in the literature showing an increased susceptibility of people living with diabetes to many bacterial or viral respiratory infections [7,8], including during the recent epidemics related to H1N1 and MERS-CoV (Middle East Respiratory Syndrome-related coronavirus) [9,10]. As the relation between diabetes and severe forms of COVID-19 is strongly suspected, it has become essential to identify more precisely the factors that expose the diabetic population to a significant excess risk of adverse progression of the infection.

After univariate analysis, the factors associated with in-hospital mortality in our diabetic patients hospitalized for COVID-19, are represented by male gender (p = 0.014), oxygen saturation on admission < 90% (p = 0.003), extent of lung injury on chest CT (p < 0.000), respiratory distress syndrome (p < 0.000), failure to take anticoagulation prior to admission (p < 0.001), transfer to reanimation (p < 0.000), and invasive ventilation (p < 0.000). In addition, other factors related to adverse progression of the Covid-19 disease in patients with non-obtained glycemic control were objectified, which are represented by not taking insulin therapy before admission (p = 0.015), and a CRP level higher than 70 mg/l (p = 0.008).

We also found in the univariate analysis that advanced age was related to in-hospital mortality in our patients (average age: 64 years (+/-12.55); p = 0.041), especially in patients whose glycemic targets were not reached (average age: 64 years (+/-11.93); p = 0.009).

In the multivariate analysis, after adjustment for other factors, we identified that in-hospital mortality in our diabetic patients hospitalized for covid-19 was explained by respiratory distress syndrome (p = 0.030), admission to reanimation (p = 0.004), and invasive ventilation (p = 0.026).

In the CORONADO study, BMI was positively and independently associated with the main judgment criterion in multivariate analysis. In addition, advanced age (higher than 75 years), history of sleep apnea syndrome, and diabetic complications (microvascular and macrovascular complications, mainly coronary heart disease) remained significantly and independently associated with death on day 7 of admission.

Also in multivariate analyses of the Coronado study, dyspnea, reduced glomerular filtration rate, increased transaminases and CRP at admission were independent markers of early death [4].

The impact of glycemic control on the prognosis of covid-19 disease in hospitalized diabetic patients is a key point, which should be analyzed differently depending on whether glycemic control is considered before hospitalization, at admission, or during hospitalization.

After multivariate analysis, we found that there was no statistically significant relation between glycemic control obtained during hospitalization and adverse progression of Covid-19 disease (p = 0.474). Moreover, glycemic control during hospitalization plays a modifying role on the effect of other factors worsening the progression of Covid-19 disease. Thus, glycemic control during hospitalization improves the effect of other factors related to the progression of Covid-19 disease.

After univariate analysis, we found that there was a statistically significant relation between glycemic control during hospitalization and female gender (p = 0.001), inaugural diabetes (p = 0.012), progression of diabetes for less than 5 years (p = 0.021), and previous glycemic control (p = 0.037).

On the other hand, there was no statistically significant relation between prior glycemic control and adverse progression of Covid-19 disease (p = 0.321), which is consistent with the results of the CORONADO study, where prior glycemic control at hospitalization, reflected by the last available HbA1c measurement in the 6 months prior to admission, did not appear to have a significant impact on the severity of Covid-19 in hospitalized people with diabetes [4].

In our study, taking into account the inflammatory parameters at admission (CRP >= 70 mg/l, and hyperleukocytosis), hyperglycemia at admission probably corresponded to a stress hyperglycemia secondary to the inflammatory reaction, and could be considered as a risk factor of severity in clinical practice. The impact of admission hyperglycemia on the prognosis of Covid-19 disease was demonstrated in a single-center Italian study, where they found that initial hyperglycemia is an independent predictor of mortality [11].

Another American multicenter study showed that severe hyperglycemia on admission (a blood glucose level of 2.50 g/l) in patients hospitalized for covid-19 in an intensive care unit was significantly associated with an increased risk of complications and mortality; thus, achieving a blood glucose level between 1.40 g/l and 1.80 g/l within 2 days of admission to the intensive care unit was associated with a reduced mortality rate [3].

Early hyperglycemia is an independent marker of mortality, increasing the risk by 7 times, which however decreased after adjustment of potential confounding factors, which are independent predictors of severe forms of COVID-19 disease, such as age, obesity, chronic kidney failure, arterial hypertension (AH) and cardiovascular disease, which are also associated with diabetes [12]. This association was not found in the CORONADO cohort, where the relation between admission hyperglycemia and risk of adverse progression leading to death was no longer significant after multivariate analysis [4].

However, retrospective data from a Chinese observational study on 7337 COVID-19 patients showed a statistically significant relation between glycemic control during hospitalization (variability between 0.70 and 1.80 g/L versus > 1.80 g/L) and mortality reduction of 1.1% versus 11%. However, this study has several limitations that require critical reading regarding the methodology of statistical analysis, including the retrospective nature of the study that does not allow to determine whether active control of glycemic thresholds to normal values could improve the progression of Covid-19 disease; the inclusion criteria, so all data were obtained from cohorts of patients admitted to various hospitals, therefore, the effect of glycemic control may be different in patients with Covid-19 and outpatient diabetes or in ethnically or geographically diverse populations; the inability to recover pre-hospital diabetes status due to the urgent circumstances of the COVID-19 pandemic, as pre-hospital diabetes status could be significantly associated with many clinical parameters, which are known independent risk factors for poor progression of COVID-19, including cardiovascular abnormalities and immune dysfunction; also the number of diabetic patients with good glycemic control was low (282 patients versus 528) and may not be influential enough to reflect the overall complexity of the general population [13].

Conclusion

Our study allowed us to establish that the relation between glycemic control during hospitalization and the adverse progression of Covid-19 disease was no longer significant after multivariate analysis. The glycemic control, thus plays a modifying role on the effect of the other factors aggravating the progression of Covid-19, in particular the respiratory distress syndrome, the transfer to reanimation and the invasive ventilation.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

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