Cardiometabolic therapy and mortality in very old patients with diabetes hospitalized due to COVID-19

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Abstract

Background: The effects of cardiometabolic drugs on the prognosis of diabetic patients with COVID-19, especially very old patients, are not well-known. This work aims to analyze the association between preadmission cardiometabolic therapy (antidiabetic, antiaggregant, antihypertensive, and lipid-lowering drugs) and in-hospital mortality among patients ≥80 years with type 2 diabetes mellitus hospitalized for COVID-19.

Methods: We conducted a nationwide, multicenter, observational study in patients ≥80 years with type 2 diabetes mellitus hospitalized for COVID-19 between March 1 and May 29, 2020. The primary outcome measure was in-hospital mortality. A multivariate logistic regression analysis were performed to assess the association between preadmission cardiometabolic therapy and in-hospital mortality.

Results: Of the 2,763 patients ≥80 years old hospitalized due to COVID-19, 790 (28.6%) had T2DM. Of these patients, 385 (48.7%) died during admission. On the multivariate analysis, the use of dipeptidyl peptidase-4 inhibitors (AOR 0.502, 95%CI 0.309-0.815, p=0.005) and angiotensin receptor blockers (AOR 0.454, 95%CI 0.274-0.759, p=0.003) were independent protectors against in-hospital mortality whereas the use of acetylsalicylic acid was associated with higher in-hospital mortality (AOR 1.761, 95%CI 1.092-2.842, p=0.020). Other antidiabetic drugs, angiotensin-converting enzyme inhibitors and statins showed neutral association with in-hospital mortality.

Conclusions: We found important differences between cardiometabolic drugs and in-hospital mortality in older patients with type 2 diabetes mellitus hospitalized for COVID-19. Preadmission treatment with dipeptidyl peptidase-4 inhibitors and angiotensin receptor blockers could reduce in-hospital mortality; other antidiabetic drugs, angiotensin-converting enzyme inhibitors and statins seem to have a neutral effect; and acetylsalicylic acid could be associated with excess mortality.

Key words: age ≥80, type 2 diabetes, coronavirus disease-2019, mortality, cardiometabolic therapy

Introduction

Aging is one of the most significant factors associated with a poor prognosis in coronavirus disease-2019 (COVID-19) (1-4). In addition, diabetes is a common comorbidity among patients with severe COVID-19 (5,6) and while it is not known to increase susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, it has also been correlated with a more severe course of COVID-19 (7,8).

As expectations of specific antiviral and immunological therapies for the management of COVID-19 have dimmed (9), drugs used for controlling cardiovascular risk factors have emerged as having a potentially important role in the approach to patients with COVID-19. In this sense, some studies have suggested possible protective effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) (10,11), statins (12,13), acetylsalicylic acid (ASA) (14), dipeptidyl peptidase-4 inhibitors (DPP-4i) (15), and metformin (16), although these findings are based on observational studies and in vitro data, and their conclusions are controversial (3,17-19).

Our aim was to analyze the association between preadmission cardiometabolic therapy (antidiabetic, antiaggregant, antihypertensive, and lipid-lowering drugs) with in-hospital mortality in patients ≥80 years with type 2 diabetes mellitus (T2DM) hospitalized due to COVID-19.

Patients and methods

Study Design and Population

We conducted an observational, multicenter, nationwide study of patients ≥80 years of age with T2DM hospitalized with COVID-19 in Spain from March 1 to May 29, 2020. All patient data was obtained from the Spanish Society of Internal Medicine's SEMI-COVID-19 Registry, in which 160 hospitals in Spain participate. The SEMI-COVID-19 Registry retrospectively compiles data on the first admission of patients ≥18 years of age with COVID-19 confirmed microbiologically by a reverse transcription polymerase chain reaction (RT-PCR) test. More in-depth information on the justification, objectives, methodology, and preliminary results of the SEMI-COVID-19 Registry have recently been published (6).

Definition of variables

Patients were considered to have T2DM if this diagnosis was recorded on their electronic medical record and they were treated with antidiabetic drugs. We analyzed the use of antidiabetic drugs (metformin, DPP-4i, insulin, sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP-1ra), antiaggregant drugs (ASA), antihypertensive drugs (ACEI, ARB), and statins. All pre-admission comorbidities were collected from patients' electronic medical records, which were obtained from each hospital. In-hospital mortality was the primary outcome

variable. More in-depth information about the definition of other variables has recently been reported in manuscripts published by the SEMI-COVID-19 Network (4,6).

The severity grade of COVID-19 disease was established according to the patient's clinical condition: mild grade (symptoms without evidence of pneumonia or hypoxia), moderate grade (clinical signs of pneumonia but not signs of severe pneumonia, including basal oxygen saturation ≥92%), severe grade (clinical signs of pneumonia plus one of the following: basal oxygen saturation <92%; resting respiratory rate >30 breaths/minute; severe respiratory distress), and critical grade (sepsis or shock with acute respiratory distress syndrome and/or multiple organ dysfunction or failure).

Statistical analysis

Patients were divided into two groups: survivors and non-survivors. The characteristics of each group were analyzed using descriptive statistics. Continuous and categorical variables were expressed as medians and interquartile ranges (IQR) and as absolute values and percentages, respectively. The differences between groups were calculated using the Mann-Whitney U test for continuous variables and Pearson's chi-square test for categorical variables. Values were considered to be statistically significant when $p<0.05$.

A multivariate analysis was performed to control for confounding variables. The regression analysis values were expressed as adjusted odds ratios (AOR) with a 95% confidence interval (CI). A multiple logistic regression analysis was used to identify independent variables of in-hospital mortality. In order to select the variables, the forward selection Wald statistic was used. Variables analyzed in the model were: demographics (age, sex, acquisition), body mass index, comorbidities and dependence (degree of dependence, Charlson Comorbidity Index, hypertension, dyslipidemia, coronary disease, cerebrovascular disease, peripheral vascular disease, atrial fibrillation, heart failure, dementia, chronic lung disease, obesity, malignancy, moderate-to-severe renal disease), symptoms (dyspnea),

physical examination (oxygen saturation <90%, temperature 37.8ºC, tachycardia, quick sequential organ failure assessment score ≥2), severity grade of COVID-19 disease, laboratory findings (neutrophils, lymphocytes, hemoglobin, platelet count, glucose, estimated glomerular filtration rate, lactate dehydrogenase, c-reactive protein, alanine aminotransferase), and treatment (metformin, DPP-4i, insulin, SGLT-2i, GLP-1ra, ASA, ACEI, ARB and statin). Discrimination of the fitted logistic model was assessed via a receiver operating characteristic (ROC) curve. The Hosmer-Lemeshow test for logistic regression was used to determine the model's goodness of fit. Due to the fact that there were some missing values, variables which were not recorded for >25% of patients were excluded from the analysis. These included serum ferritin, D-dimer, interleukin-6, procalcitonin, venous lactate, and aspartate aminotransferase. Statistical data analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp).

Ethics approval and consent to participate

The STROBE statement guidelines were followed in the conduct and reporting of the study. All patients gave their informed consent. When there were biosafety concerns and/or when the patient had already been discharged, verbal informed consent was requested and noted on the medical record. Data confidentiality and patient anonymity were maintained at all times, in accordance with Spanish regulations on observational studies. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of Málaga on March 27, 2020 (Ethics Committe code: SEMI-COVID-19 27-03-20), as per the guidelines of the Spanish Agency of Medicines and Medical Products.

Results

Baseline clinical characteristics, presentation, and laboratory data

Of the 2,763 patients ≥80 years old identified, 790 (28.6%) had T2DM. Figure 1 shows the patient inclusion flowchart for this study. A total of 385 patients (48.7%) died during admission. Baseline clinical characteristics, clinical presentation, and laboratory data of patients grouped by non-survivors and survivors are shown in Table 1. The percentages of females in the non-survivor and survivor groups were 43.2% and 51.0%, respectively (p=0.03). The percentages of patients with moderate and severe dependency in the non-survivor group were higher than in the survivor group (52.6% vs. 44.8%, p<0.001). The median Charlson Comorbidity Index value and prevalence of comorbidities were similar in the survivor and non-survivor groups, with the exception of dementia (37.9% vs 30.2%, p=0.03). The presence of dyspnea, pulse oximetry <90%, fever, tachycardia, and qSOFA ≥ 2 were more common in the non-survivor group. In terms of laboratory values, a higher proportion of patients in the non-survivor group had high admission values of leukocytes, neutrophils, plasma glucose, lactate dehydrogenase, aminotransferases, C-reactive protein, lactate, procalcitonin, ferritin, and D-dimer (p<0.05) and low estimated glomerular filtration rate (eGFR) and lymphocyte values.

Preadmission cardiometabolic therapy

Preadmission cardiometabolic therapy of patients grouped by non-survivors and survivors is shown in Table 2. The antidiabetic drugs used before admission were similar between the non-survivor and survivor groups except for DDP-4i, which were used in 28.9% of non-survivors and 36.2% of survivors (p=0.03). Statin and ARB use were less frequent in non-survivors than in survivors (49.2% and 7.1% versus 56.6% and 19.8%, respectively, p<0.05) while the use of antiaggregants was similar in both groups.

Associations between preadmission cardiometabolic drugs and in-hospital mortality

On the multivariate analysis, the preadmission cardiometabolic medications found to be independent protective factors against in-hospital mortality were the use of DPP-4i (AOR 0.502, 95% CI 0.309-0.815, p=0.005) and ARB (AOR 0.454, 95% CI 0.274-0.759, p=0.003) while the use of ASA was associated with greater in-hospital mortality (AOR 1.761, 95% CI 1.092-2.842, p=0.020). Metformin (AOR 0.976, 95% CI 0.639-1.788, p=0.792), insulin (AOR 1.308, 95% CI 0.679-2.476, p=0.576), SGLT-2i (AOR 0.812, 95% CI 0.755-1.988, p=0.401), GLP-1ra (AOR 0.912, 95% CI 0.501-1.896, p=0.512), ACEI (AOR 1.048, 95% CI 0.841-1.991, p=0.186), and statins (AOR 0.917, 95% CI 0.723-1.978, p=0.335) showed neutral association with in-hospital mortality. In this model, the goodness-of-fit showed a p-value of 0.142 (Hosmer-Lemeshow test) and the area under the ROC curve was 0.788 (discrimination). Associations between preadmission cardiometabolic drugs and in-hospital mortality are shown in Table 3.

Discussion

The COVID-19 pandemic has affected older, frail individuals with diabetes particularly severely and there is still no effective treatment for COVID-19 available. Therefore, we performed a multicenter, nationwide, retrospective, observational study to analyze the impact of preadmission cardiometabolic medication on mortality in very old patients with T2D hospitalized for COVID-19.

Our study suggests that preadmission treatment with DPP-4i and ARB could be associated with reduced in-hospital mortality in very old patients with T2DM hospitalized for COVID-19 whereas treatment with ASA could be associated with excess mortality. Other antidiabetic drugs, ACEI, and statins showed neutral association with mortality.

So far, there has been no conclusive evidence in regard to the potential implications of cardiometabolic therapies on COVID-19 outcomes, especially among older patients. Additionally, whether certain antidiabetic drugs can improve the prognosis of diabetic patients with COVID-19 remains unknown. Studies on glucose-lowering drugs in patients hospitalized with COVID-19 have shown conflicting results. In some reports, the use of oral antidiabetics had a neutral effect on in-hospital mortality and the composite outcome of poor prognosis, defined as progression to severe or critical illness and in-hospital death (19,20), whereas in other studies, metformin had a beneficial effect on clinical outcomes (16,18). Insulin use was associated with a greater risk of poor prognosis compared to not using it (20,21).

In our study, which was conducted solely in very old patients with T2DM, all antidiabetic therapies showed neutral effects on the clinical outcomes of COVID-19 with the notable exception of DPP-4i which, after exhaustive adjustment for potential confounding factors, were associated with a significant reduction in in-hospital deaths. Overall, data from human studies on the effects of DPP-4i

in COVID-19 are scarce. Better clinical outcomes in patients with T2DM and COVID-19 have also been reported in a population-based study of 832 patients from the National Health Review and Assessment Service database in Korea (22).

In a recent multicenter, case-control, retrospective, observational study of 338 patients with T2DM admitted to hospitals in northern Italy for COVID-19, sitagliptin treatment in conjunction with insulin administration upon admission was determined to be associated with reduced mortality and improved clinical outcomes when compared to standard of care (15). These potential benefits of DPP-4i in patients with T2DM and COVID-19 must be confirmed in further research and placebo-controlled trials. Currently, there are two ongoing trials analyzing the safety and efficacy of linagliptin in patients with T2DM hospitalized for COVID-19 (NCT04542213, NCT04371978).

Several possible mechanisms have been proposed to explain the potential benefits of DPP-4i in individuals with T2DM and COVID-19 (23-25). First, T2DM is characterized by an overexpression of DPP-4 receptors, thus their inhibition may have immunoregulatory and anti-inflammatory effects (26,27). Second, aging is associated with changes in cellular and humoral immunity that could favor worse outcomes in COVID-19 (28). Third, DPP-4 has been identified as a receptor for MERS-CoV (22) and, additionally, the structure of SARS-CoV-2 spike glycoprotein S1, which mediates virus entry into the host cell, has high degree of homology with DPP-4 and angiotensin-converting enzyme 2 (ACE2) (29). This may indicate that DPP-4 can facilitate SARS-CoV-2 entry into respiratory tract cells[29] and as such, DPP-4 inhibition could contribute to reducing the viral load and improving inflammatory and immune responses so as to prevent a cytokine storm, which can entail lung injury and multiple organ failure in COVID-19 (30,31).

A previous work from the SEMI-COVID-19 Network that analyzed 2,666 patients with T2DM admitted for COVID-19 did not find any significant associations between at-home glucose-lowering drugs and mortality or other adverse outcomes (19). However, the mean age of patients in that study was much younger than those in our cohort (75 vs 86 years), a fact that could explain the

difference in results. Aging may be associated with DPP-4 overexpression; a significant correlation between membrane DPP-4 activity and animal age has been found in murine models (32). It has also been reported that DPP-4 receptor levels rise on the senescent cell surface, suggesting that DPP-4 could play an important role in the aging process (33). Aging is also characterized by a state of chronic low-grade inflammation (termed "inflammaging") that could predispose patients to experiencing a cytokine storm in COVID-19. Moreover, some preclinical evidence suggests that the anti-inflammatory effects of DPP-4 may be more intense in older patients (34). Taken as a whole, these data could explain why more beneficial effects of DPP-4i are observed in older patients with T2DM and COVID-19 than in younger populations.

We found that previous treatment with ARB, but not with ACEI, in older patients with T2DM hospitalized for COVID-19 was associated with a lower risk of all-cause mortality, a finding not previously reported in this population. The role of renin-angiotensin-aldosterone system (RAAS) inhibitors in the COVID-19 has not been fully characterized. Given that both ACEI and ARB induce up-regulation of ACE2 (35), it has been hypothesized that these drugs could augment susceptibility to and severity of SARS-CoV-2 infection (36). However, data from observational studies indicate that use of RAAS inhibitors in patients with COVID-19 is safe (17,37). A large meta-analysis which analyzed 28,872 patients and examined critical events and mortality data on patients prescribed ACEI and ARB found that their chronic use, especially among hypertensive patients with COVID-19, had beneficial effects (38). In view of the foregoing, continuing ACEI and ARB treatment in COVID-19 patients has been recommended (39).

In spite of its upregulation of ACE2, the potential benefits of RAAS inhibitor treatment in COVID-19 could be explained through its enhancement of the ACE2/Ang1−7/Mas axis. It converts angiotensin II into Ang1−7, which has anti-inflammatory properties that preclude lung injury due to COVID-19 (40,41). Aging is associated with an upregulation of the angiotensin II proinflammatory pathway as

well as a decrease in ACE2 levels and this likely predisposes older individuals with diabetes to more severe COVID-19 disease (42).

Since ARB act on the final step of the RAAS system, blocking the AT1 receptor of angiotensin II, it has been postulated that they might be superior to ACEI in terms of improving COVID-19 prognosis (43). In fact, better outcomes have been described in patients with COVID-19 and hypertension who receive ARB versus ACEI (11). Until more evidence is available, it would be wise to prioritize the use of ARB over ACEI in this population.

This work also found that preadmission therapy with ASA was associated with increased in-hospital mortality in very old patients with diabetes hospitalized for COVID-19. One retrospective study concluded that ASA use may have protective effects on the lungs and reduce the need for mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized COVID-19 patients (14). This is likely related to the antithrombotic and anti-inflammatory properties of ASA. However, in that work, the mean age of ASA-treated patients was 62 years and only 55% had diabetes, so these results cannot be extrapolated to older diabetic patients.

The impact of ASA use on all-cause mortality in older patients is uncertain, as both favorable and unfavorable effects have been reported (44,45). In the ASPREE trial (45), which analyzed healthy patients ≥70 years of age, low-dose aspirin significantly increased the risk of major bleeding events and mortality. In light of this finding, the potential benefits of ASA use must be weighed against the risk of hemorrhage and other adverse effects in older individuals with diabetes, especially those without prior cardiovascular disease (46).

Finally, preadmission therapy with statins showed a neutral effect on mortality in our population. It has been postulated that statins could have a potential role as an adjunct therapy in COVID-19 to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 (47). A possible antiviral effect of statins has also been postulated (48).

A meta-analysis (12) and two observational studies (13,49) -one of them in diabetic population (13)- have reported a significant reduction in mortality in patients with COVID-19 who received statins before admission. In another study, in-hospital statin use was linked to a reduced risk of mortality in individuals with COVID-19 (50). Once again, the mean age of patients included in these studies was significantly younger than in our population, so this potential benefit may not exist in older patients.

Our findings are important because they provide valuable information on the role of preadmission cardiometabolic medication on mortality in very old patients with T2D hospitalized for COVID-19. It is well known that both advanced age and T2D may negatively impact clinical outcomes in patients with COVID-19 (4,5,19). In addition, data were collected in a large multicenter, nationwide study and a robust multiple logistic regression analysis was used to identify independent variables of in-hospital mortality. Nevertheless, these results should be considered within the context of several potential limitations. First, its observational design does not allow us to determine causal relationships. Although, regional university hospitals were the principal collaborators in our registry, providing the majority of COVID-19 patients, and a short period (from March 1 to May 29, 2020) was analyzed, the possible effects of hospital category and date of hospitalization cannot be fully excluded. Additional randomized controlled trials are needed to evaluate confounding factors that were potentially overlooked in our study. Second, our study was conducted in very old patients with diabetes hospitalized with severe SARS-CoV-2 infection and thus its conclusions cannot be extrapolated to other populations with COVID-19. Third, we did not have data on the characteristics of patients' T2DM, such as glycemic control before hospitalization, duration of diabetes, blood glucose levels during hospitalization, or in-hospital anti-hyperglycemic management. Lastly, the data provided about at-home glucose-lowering drugs did not include information on treatment adherence or treatment duration.

Conclusion

We found important differences between cardiometabolic drugs and outcomes in older patients with T2DM hospitalized for COVID-19. Preadmission treatment with DPP-4i and ARB could reduce in-hospital mortality; other antidiabetic drugs, ACEI and statins seem to have a neutral effect; and ASA could be associated with excess mortality. These findings, which could have important clinical implications, must be confirmed in further controlled trials.

Conflict of interest

None declared.

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Authors' contributions

JMRR contributed to the conception, design of the work the acquisition, interpretation of data, writing-original draft preparation, writing-review and editing, and supervision. FJCS, SJC, MDSB, JBF, MPA, CAC, MBC, MMB, IFM, AGG, FNR, CTA, GMN, AGN, AHM, GMGG, JNAP, VHG, LCG, PCC, HMM, and JMCR made contributions to the acquisition of data and revised the work. LMPB contributed to interpretation of data, writing-review and editing, and supervision. RGH was a major contributor in interpretation of data, writing-original draft preparation, writing-review and editing, and supervision. All authors read and approved the final manuscript.

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Table 1. Baseline clinical characteristics, clinical presentation, and laboratory data of patients ≥80 years with type 2 diabetes mellitus hospitalized due to COVID-19 grouped by non-survivors and survivors.

	Missing	Non-survivors (n=385)	Survivors (n=405)	p-value
Age, years		86 (82.7-88.9)	85.8 (82.7-88.9)	0.477
Sex, female	2	166 (43.2)	206 (51.0)	0.029
Acquisition	5			0.124
Community		266 (69.8)	281 (69.6)	
Nosocomial		41 (10.8)	29 (7.2)	
Nursing home		74 (19.4)	94 (23.3)	
Comorbidities and dependence				
Moderate-severe functional dependence	10	219 (57.6)	179 (44.8)	<0.001
CCI	30	7 (6-9)	7 (6-8)	0.110
Hypertension	1	319 (82.6)	347 (85.9)	0.204
Dyslipidemia	0	250 (64.9)	272 (67.2)	0.509
Dementia	1	144 (37.4)	122 (30.2)	0.032

Atrial fibrillation	1	111 (28.8)	111 (27.5)	0.672
Coronary artery disease	3	80 (20.8)	70 (17.4)	0.213
Cerebrovascular disease	4	82 (21.4)	71 (17.7)	0.192
Peripheral vascular disease	2	53 (13.8)	42 (10.4)	0.150
Heart failure	4	83 (21.6)	75 (18.7)	0.301
Chronic obstructive pulmonary disease[Φ]	4	65 (16.9)	75 (18.7)	0.526
Obesity[ΦΦ]	94	74 (22.2)	66 (18.2)	0.184
Malignancy[ΦΦΦ]	4	63 (16.4)	43 (10.7)	0.118
Moderate-to-severe chronic kidney disease	5	73 (19.1)	63 (15.7)	0.210
Clinical presentation				
Dyspnea	2	270 (70.3)	212 (52.5)	<0.001
Oxygen saturation <90%	18	143 (38.1)	55 (13.9)	<0.001
Temperature ≥37.8ºC	49	95 (26.3)	59 (15.5)	<0.001
Tachycardia (>100 beats per minute)	27	98 (26.4)	62 (15.8)	<0.001
qSOFA score ≥2	0	122 (31.7)	52 (12.8)	<0.001
Laboratory data				
Leukocytes (10^3/μL)	11	7.82 (5.82-10.81)	6.73 (0.50-8.72)	<0.001
Neutrophils (10^3/μL)	16	6.39 (4.64-9.08)	4.85 (3.40-6.88)	<0.001
Lymphocytes (10^3/μL)	14	0.80 (0.50-	0.96 (0.70-	<0.001

		1.21)	1.30)	
Hemoglobin (g/dL)	11	12.9 (11.3-14.1)	12.7 (11.3-13.8)	0.342
Platelet count ($10^3/\mu L$)	11	186 (143-245)	186 (127-246)	0.642
Glucose (mg/dL)	38	176 (139-237)	146 (116-203)	<0.001
eGFR ($ml/min/1.73m^2$)	18	41.35 (27.9-60.3)	51.7 (35.8-69.7)	<0.001
Lactate dehydrogenase (U/L)	157	380 (288-524)	284 (219-373)	<0.001
AST (U/L)	223	36 (25-57)	27 (20-39)	<0.001
ALT (U/L)	99	25.5 (16-36)	20 (14-29)	0.010
C-reactive protein (mg/dL)	38	117 (52-198)	50 (19-111)	<0.001
Venous lactate (mmol/L)	412	2.0 (1.4-3.0)	1.6 (1.2-2.50)	0.002
Procalcitonin (ng/mL)	407	0.23 (0.12-0.65)	0.12 (0.07-0.22)	<0.001
Interleukin-6 (pg/mL)	719	47.3 (25.2-100)	20.8 (9.0-65.1)	0.015
D-dimer (ng/mL)	404	1310 (713-3270)	1026 (586-2105)	0.010
Ferritin /µg/L	519	582 (285-1287)	359 (179-707)	<0.001

pH	341	7.43 (7.39-7.47)	7.44 (7.39-7.47)	0.358
pCO_2 (mmHg)	351	35.8 (30.8-41.0)	35.8 (31.2-41.8)	0.265
pO_2 (mmHg)	364	58.5 (51.0-69.5)	68.0 (57.0-80.5)	<0.001
pO_2/FiO_2 ratio	383	247 (184-296)	290 (248-342)	<0.001

Values are shown as medians and interquartile ranges and as absolute values and percentages, respectively. Values were considered to be statistically significant when $p<0.05$.

$^{\Phi}$Chronic pulmonary disease includes chronic obstructive pulmonary disease and/or asthma.

$^{\Phi\Phi}$Obesity: body mass index $\geq$30 kg/m^2.

$^{\Phi\Phi\Phi}$Malignancy includes solid tumors or hematologic neoplasms.

CCI: Charlson comorbidity index; IQR: interquartile range; qSOFA: quick sequential organ failure assessment.

Table 2. Preadmission cardiometabolic medications of patients ≥80 years with type 2 diabetes mellitus hospitalized due to COVID-19 grouped by non-survivors and survivors.

	Missing	Non-survivors (n=385)	Survivors (n=405)	p-value
Antidiabetic drugs				
Metformin	1	206 (53.5)	214 (53.0)	0.880
DPP-4i	15	110 (28.9)	143 (36.2)	0.031
Insulin	14	103 (27.2)	108 (27.2)	0.993
SGLT-2i	13	17 (4.5)	15 (3.8)	0.626
GLP-1ra	13	11 (2.9)	13 (3.3)	0.755
Lipid-lowering drugs				
Statin	7	188 (49.2)	227 (56.6)	0.038

Antihypertensive drugs				
ACEI	15	44 (11.6)	52 (13.1)	0.538
ARB	12	27 (7.1)	79 (19.8)	<0.001
Antiaggregant drugs				
ASA	7	132 (34.6)	132 (29.6)	0.131

Values are shown as absolute values and percentages. Values were considered to be statistically significant when $p<0.05$.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ASA: acetylsalicylic acid; DDP-4i: Dipeptidyl peptidase-4 inhibitor; GLP-1ra: Glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium-glucose linked transporter-2 inhibitor.

Table 3. Associations between preadmission cardiometabolic drugs and in-hospital mortality in patients ≥80 years with type 2 diabetes mellitus hospitalized due to COVID-19

	AOR (95% CI)	p-value
Metformin	0.976 (0.639-1.788)	0.782
DPP-4i	0.502 (0.309-0.815)	0.005
Insulin	1.308 (0.679-2.476)	0.579
SGLT-2i	0.812 (0.755-1.988)	0.401
GLP-1ra	0.912 (0.501-1.896)	0.521
ASA	1.761 (1.092-2.842)	0.020
ACEI	1.048 (0.841-1.991)	0.186
ARB	0.454 (0.274-0.759)	0.003
Statins	0.917 (0.723-1.978)	0.335
Hosmer-Lemeshow test		0.144
AUC	0.788 (0.750-0.826)	0.001

A multivariate logistic regression analysis were performed to assess the association between preadmission cardiometabolic therapy and in-hospital mortality, controlling for confounding variables. The regression analysis values were expressed as adjusted odds ratios with a 95% confidence interval. In order to select the variables, the forward selection Wald statistic was used. Variables analyzed in the model were: demographics (age, sex, acquisition), body mass index, comorbidities and dependence (degree of dependence, Charlson Comorbidity Index, hypertension, dyslipidemia, coronary disease, cerebrovascular disease, peripheral vascular disease, atrial fibrillation, heart failure, dementia, chronic lung disease, obesity, malignancy, moderate-to-severe renal disease), symptoms (dyspnea), physical examination (oxygen saturation <90%, temperature

37.8ºC, tachycardia, quick sequential organ failure assessment score ≥2), severity grade of COVID-19 disease, laboratory findings (neutrophils, lymphocytes, hemoglobin, platelet count, glucose, estimated glomerular filtration rate, lactate dehydrogenase, c-reactive protein, alanine aminotransferase), and treatment (metformin, DPP-4i, insulin, SGLT-2i, GLP-1ra, ASA, ACEI, ARB and statin). Discrimination of the fitted logistic model was assessed via a receiver operating characteristic (ROC) curve. The Hosmer-Lemeshow test for logistic regression was used to determine the model's goodness of fit. Due to the fact that there were some missing values, variables which were not recorded for >25% of patients were excluded from the analysis. These included serum ferritin, D-dimer, interleukin-6, procalcitonin, venous lactate, and aspartate aminotransferase. Values were considered to be statistically significant when $p<0.05$.

ACEI: angiotensin-converting enzyme inhibitor; AOR: adjusted odds ratios; ARB: angiotensin receptor blocker; ASA: acetylsalicylic acid; CI: confidence interval; DDP-4i: Dipeptidyl peptidase-4 inhibitor**;** eGFR: estimated glomerular filtration rate; GLP-1ra: glucagon-like peptide-1 receptor agonist; qSOFA: quick sequential organ failure assessment; SGLT-2i: sodium-glucose cotransporter 2 inhibitors

Figure 1