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

Jose Manuel Ramos-Rincón, MD PhD1†, Luis M. Pérez-Belmonte, MD PhD2∗, Francisco Javier Carrasco-Sánchez, MD PhD3, Sergio Jansen-Chaparro, MD PhD4, Mercedes De-Sousa-Baena, MD5, José Bueno-Fonseca, MD4, Maria Pérez-Aguilar, MD3, Coral Arévalo-Cañas, MD4, Marta Bacete Cebrian, MD5, Manuel Méndez-Bailón, MD PhD6, Isabel Fiteni Mera, MD, PhD7, Andrés González García, MD PhD6, Francisco Navarro Romero, MD PhD9, Carlota Tuñón de Almeida, MD10, Gemma Muñiz Nicolás, MD11, Amara González Noya, MD12, Almudena Hernández Milian, MD13, Gema María García García, MD14, José Nicolás Alcalá Pedrajas, MD15, Virginia Herrero García, MD16, Luis Corral-Gudino, MD PhD17, Pere Comas Casanova, MD18, Héctor Meijide Míguez, MD PhD19, José Manuel Casas-Rojo, MD20, Ricardo Gómez-Huelgas, MD PhD21; for the SEMI-COVID-19 Network**.

1Department of Clinical Medicine, Miguel Hernandez University of Elche, Alicante, Spain.

2Internal Medicine Department, Regional University Hospital of Málaga, Biomedical Research Institute of Málaga (IBIMA), University of Málaga (UMA), Málaga, Spain.

3Internal Medicine Department. Juan Ramón Jiménez University Hospital, Huelva, Spain.

4Internal Medicine Department, 12 de Octubre University Hospital, Madrid, Spain.

5Internal Medicine Department, Gregorio Marañón University Hospital, Madrid, Spain.

6Internal Medicine Department, San Carlos Clinical Hospital, Complutense University, Madrid, Spain.

© The Author(s) 2021. Published by Oxford University Press on behalf of The Gerontological Society of America. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.
7 Internal Medicine Department, Royo Villanova Hospital, Zaragoza, Spain.

8 Internal Medicine Department, Ramón y Cajal University Hospital, Madrid, Spain.

9 Internal Medicine Department, Costa del Sol Hospital, Marbella (Málaga), Spain.

10 Internal Medicine Department, Zamora Hospital Complex, Zamora, Spain.

11 Internal Medicine Department, Virgen de la Salud Hospital, Toledo, Spain.

12 Internal Medicine Department, Ourense University Hospital Complex, Ourense, Spain.

13 Internal Medicine Department, Son Llàtzer University Hospital, Palma de Mallorca, Spain.

14 Internal Medicine Department, Badajoz University Hospital Complex, Badajoz, Spain.

15 Internal Medicine Department, Pozoblanco Hospital, Pozoblanco (Córdoba), Spain.

16 Internal Medicine Department, Doctor José Molina Orosa Hospital, Arrecife (Lanzarote), Spain.

17 Internal Medicine Department, Río Hortega University Hospital, Regional Health Management of Castilla y Leon (SACYL), Valladolid University, Valladolid, Spain.

18 Internal Medicine Department, Blanes Hospital, Blanes (Girona), Spain.

19 Internal Medicine Department, Quironsalud A Coruña Hospital, A Coruña, Spain.

20 Internal Medicine Department, Infanta Cristina University Hospital, Parla (Madrid), Spain.

†These authors have contributed equally to this work.
*Corresponding authors information:

Luis M. Pérez-Belmonte. Address: Servicio de Medicina Interna, Hospital Regional Universitario de Málaga. Avenida de Carlos Haya, s/n, 29010, Málaga, Spain. Telephone number: 0034 951 291 169. Fax number: 0034 951 290 006. E-mail address: luismiguelpb1984@gmail.com.
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 37.8°C, 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 cells29 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.

Funding

None declared.

Acknowledgments

We thank Claire Alexandra Conrad for her help with the final English-language version and the SEMI-COVID-19 Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support.

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.
References

1. Docherty AB, Harrison EM, Green CA, et al; ISARIC4C investigators. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985. doi: 10.1136/bmj.m1985.

2. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966. doi: 10.1136/bmj.m1966

3. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M; SARS-RAS Investigators. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension. 2020;76:366-372. doi: 10.1161/HYPERTENSIONAHA.120.15324.

4. Ramos-Rincon JM, Buonaiuto V, Ricci M, et al; SEMI-COVID-19 Network. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. J Gerontol A Biol Sci Med Sci. 2020;glaa243. doi: 10.1093/gerona/glaa243.

5. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95. doi: 10.1016/j.ijid.2020.03.017.

6. Casas Rojo JM, Antón Santos JM, Millán Núñez-Cortés J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. Rev Clin Esp. 2020;220:480-494. doi: 10.1016/j.rce.2020.07.003.
7. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020;43:867-869. doi: 10.1007/s40618-020-01236-2.

8. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020;8:782-792. doi: 10.1016/S2213-8587(20)30238-2.

9. Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379. doi: 10.1136/bmj.m3379.

10. Baral R, White M, Vassiliou VS. Effect of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. Curr Atheroscler Rep. 2020;22:61. doi: 10.1007/s11883-020-00880-6.

11. Rodilla E, Saura A, Jiménez I, et al. Association of hypertension with all-cause mortality among hospitalized patients with COVID-19. J Clin Med. 2020;9:E3136. doi: 10.3390/jcm9103136.

12. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. Am J Cardiol. 2020;134:153-155. doi: 10.1016/j.amjcard.2020.08.004.

13. Saeed O, Castagna F, Agalliu I, et al. Statin Use and In-Hospital Mortality in Diabetics with COVID-19. J Am Heart Assoc. 2020:e018475. doi: 10.1161/JAHA.120.018475.

14. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. Anesth Analg. 2020 Oct 21. doi: 10.1213/ANE.0000000000005292.

15. Solerte SB, D’Addio F, Trevisan R, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. Diabetes Care. 2020:dc201521. doi: 10.2337/dc20-1521.
16. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol. 2020 Sep 9. doi: 10.1002/jmv.26498.

17. Fosbøl EL, Butt JH, Østergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA. 2020;324:168-177. doi: 10.1001/jama.2020.11301.

18. Bramante C, Ingraham N, Murray T, et al. Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. medRxiv. 2020:2020.06.19.20135095.

19. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD, et al; for the SEMI-COVID-19 Network. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Medicine. 2020;18:359. doi: 10.1186/s12916-020-01832-2.

20. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care. 2020;43:1399-1407. doi: 10.2337/dc20-0660.

21. Yu B, Li C, Sun Y, Wang DW. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. Cell Metab. 2020;S1550-4131(20)30647-1. doi: 10.1016/j.cmet.2020.11.014.

22. Rhee SY, Lee J, Nam H, Kyoung DS, Kim DJ. Effects of a DPP-4 inhibitor and RAS blockade on clinical outcomes of patients with diabetes and COVID-19. medRxiv. 2020;05.20.20108555.

23. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020;41:bnaa011. doi: 10.1210/endrev/bnaa011.
24. Solerte SB, Di Sabatino A, Galli M, Fiorina P. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. Acta Diabetol. 2020;57:779-83. doi: 10.1007/s00592-020-01539-z.

25. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020;8:546- 550. doi: 10.1016/S2213-8587(20)30152-2.

26. Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antinflammatory action. J Clin Endocrinol Metab. 2012;97:3333-3341. doi: 10.1210/jc.2012-1544.

27. Pinheiro MM, Stoppa CL, Valduga CJ, et al. Sitagliptin inhibit human lymphocytes proliferation and Th1/Th17 differentiation in vitro. Eur J Pharm Sci. 2017;100:17-24. doi: 10.1016/j.ejps.2016.12.040.

28. Cunha LL, Perazzo SF, Azzi J, Cravedi P, Riella LV. Remodeling of the immune response with aging: immunosenescence and its potential impact on COVID-19 immune response. Front Immunol. 2020;11:1748. doi: 10.3389/fimmu.2020.01748.

29. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full- length human ACE2. Science. 2020;367:1444-1448. doi: 10.1126/science.abb2762.

30. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020;162:108125. doi: 10.1016/j.diabres.2020.108125.

31. Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19?. Diabetes Metab Res Rev. 2020;e3330. doi: 10.1002/dmrr.3330.

32. Detel D, Baticic L, Varljen J. The influence of age on intestinal dipeptidyl peptidase IV (DPP IV/CD26), disaccharidases, and alkaline phosphatase enzyme activity in C57BL/6 mice. Exp Aging Res. 2008;34:49-62. doi: 10.1080/03610730701761957.
33. Kim KM, Noh JH, Bodogai M, et al. Identification of senescent cell surface targetable protein DPP4. Genes Dev. 2017;31:1529-1534. doi: 10.1101/gad.302570.117.

34. Omar BA, Vikman J, Winzell MS, et al. Enhanced beta cell function and anti-inflammatory effect after chronic treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin in an advanced-aged diet-induced obesity mouse model. Diabetologia. 2013;56:1752-1760. doi: 10.1007/s00125-013-2927-8.

35. Furuhashi M, Moniwa N, Mita T, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens. 2015;28:15-21. doi: 10.1093/ajh/hpu086.

36. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. Lancet Respir Med. 2020;8:e21. doi: 10.1016/S2213-2600(20)30116-8.

37. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the risk of Covid-19. N Engl J Med. 2020;382:2431-2440. doi: 10.1056/NEJMo2006923.

38. Baral R, White M, Vassiliou VS. Effect of Renin-Angiotensin-Aldosterone System inhibitors in patients with COVID-19: a systematic review and meta-analysis of 28,872 patients. Curr Atheroscler Rep. 2020;22:61. doi: 10.1007/s11883-020-00880-6.

39. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns reusing RAAS antagonists in COVID-19. March 17, 2020 (https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-reusing-raas-antagonists-in-covid-19) (European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. March 13, 2020
40. Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease, Shock. 2016;46:239-248. doi: 10.1097/SHK.0000000000000633.

41. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-879. doi: 10.1038/nm1267.

42. AlGhatrif M, Cingolani O, Lakatta EG. The dilemma of coronavirus disease 2019, aging, and cardiovascular disease: insights from cardiovascular aging science. JAMA Cardiol. 2020;5:747-748. doi: 10.1001/jamacardio.2020.1329.

43. Saavedra JM. Angiotensin receptor blockers and COVID-19, Pharmacol Res. 2020;156:104832. doi: 10.1016/j.phrs.2020.104958.

44. Loomans-Kropp HA, Pinsky P, Cao Y, Chan AT, Umar A. Association of aspirin use with mortality risk among older adult participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. JAMA Netw Open. 2019;2:e1916729. doi: 10.1001/jamanetworkopen.2019.16729.

45. McNeil JJ, Nelson MR, Woods RL, et al; ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018;379:1519-1528. doi: 10.1056/NEJMoa1803955.

46. Patel NJ, Baliga RR. Role of aspirin for primary prevention in persons with diabetes mellitus and in the elderly. Cardiol Rep. 2020;22:48. doi: 10.1007/s11886-020-01296-z.

47. Lee KCH, Sewa DW, Phua GC. Potential role of statins in COVID-19. Int J Infect Dis. 2020;96:615-617. doi: 10.1016/j.ijid.2020.05.115.
48. Reiner Z, Hatamipour M, Banach M, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci 2020;16:490-496. doi: 10.5114/aoms.2020.94655.

49. Daniels LB, Sitapati AM, Zhang J, et al. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. Am J Cardiol. 2020;136:149-155. doi: 10.1016/j.amjcard.2020.09.012.

50. Zhang XJ, Qin JJ, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metab 2020;32:176-187. doi: 10.1016/j.cmet.2020.06.015.
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     |         | 10                     | 219 (57.6)         | 179 (44.8) | <0.001 |
| dependence                     |         |                        |                    |         |
| 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 |
| Condition                                      | Group 1 | Group 2 | p-value   |
|------------------------------------------------|---------|---------|-----------|
| 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          | 4       | 65 (16.9)  | 75 (18.7)  | 0.526      |
| Obesity                                        | 94      | 74 (22.2)  | 66 (18.2)  | 0.184      |
| Malignancy                                     | 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**

| Symptom                              | Group 1 | Group 2 | p-value   |
|--------------------------------------|---------|---------|-----------|
| Dyspnea                              | 2       | 270 (70.3) | 212 (52.5) | <0.001     |
| Oxygen saturation <90%               | 18      | 143 (38.1) | 55 (13.9)  | <0.001     |
| Temperature ≥37.8°C                  | 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**

| Parameter                  | Group 1 | Group 2 | p-value   |
|----------------------------|---------|---------|-----------|
| Leukocytes (10³/µL)        | 11      | 7.82 (5.82-10.81) | 6.73 (0.50-8.72) | <0.001     |
| Neutrophils (10³/µL)       | 16      | 6.39 (4.64-9.08)  | 4.85 (3.40-6.88) | <0.001     |
| Lymphocytes (10³/µL)       | 14      | 0.80 (0.50-0.96)  | 0.96 (0.70-0.70) | <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/μL) | 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 |
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.

*Chronic pulmonary disease includes chronic obstructive pulmonary disease and/or asthma.

**Obesity: body mass index $\geq 30$ kg/m$^2$.

***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   |
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.

| 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 |
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

| Drug          | 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
37.8°C, 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
12,826 patients in the SEMI-COVID-19 Network*  

339 patients who did not meet the minimum clinical characteristics

12,487 patients who met minimum clinical characteristics  

9648 patients aged < 80 years

2,839 patients aged ≥ 80 years  

65 patients still hospitalized*  
11 patients with missing variables on diabetes

2,763 discharged patients analyzed  

790 (28.6%) patients with diabetes