PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional “Covid Data Save Lives” database study
AUTHORS	Ortega, Emilio; Corcoy, Rosa; Gratacòs, Mònica; Cos Claramunt, Francesc Xavier; Mata-Cases, Manel; Puig- Treserra, Ramon; Real, Jordi; Vlacho, Bogdan; Castelblanco, Esmeralda; Domingo, Pere; Khunti, Kamlesh; Franch-Nadal, Josep; Mauricio, Didac;

VERSION 1 – REVIEW

REVIEWER	Marfella , Raffaele University of Campania
REVIEW RETURNED	12-Apr-2021

GENERAL COMMENTS	Dear editor, In the manuscript entitled “Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19”, authors assessed the risk of severe in-hospital complications of patients admitted for coronavirus disease (COVID-19) and diabetes mellitus (DM). To date, they concluded that hyperglycaemia on admission is a strong predictor of poor outcomes, suggesting that its optimisation in a personalised manner could help to improve the outcomes 2 during the hospital stay. Following my suggestions: INTRODUCTION: Please introduce the role of ACE2 receptors in SARS/COV2 infection and in the genesis of COVID-19. In this context, as example the hypertensive patients are higher risk patients for COVID19 , ICU admission and deaths (Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of southern Italy. J Am Heart Assoc. 2020 Jul 7:e016948. doi: 10.1161/JAHA.120.016948). Please explain this point. Again, in the pathogenesis of SARS/COV2 infection, not only the ACE2 receptor but also the serin proteasis expression (TMPRSS2) is another relevant point to discuss. Indeed, as reported by authors, its expression in humans’ cells can cause the entrance and replication of SARS/COV2 (miR-98 Regulates TMPRSS2 Expression in Human Endothelial Cells: Key Implications for COVID-19. Biomedicines. 2020 Oct 30;8(11):462. doi: 10.3390/biomedicines8110462). Please describe this point and refer to the suggested reference. In my opinion these informations could improve the Introduction of your article. According to authors, I would suggest to introduce the chronic

	hyperglycemic condition (and insulin resistance), as in the case of diabetes mellitus (Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care. 2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723; Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020 Jun 11;19(1):76. doi: 10.1186/s12933-020-01047-y), but also the hospital admission hyperglycemia as a condition that increases the risk of mortality (Hyperglycaemia on admission to hospital and COVID-19. Diabetologia. 2020 Jul 6:1-2. doi: 10.1007/s00125-020-05216-2; Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005). However, please describe in detail this point. Refer to the suggested reference. However, as you could see in the current international literature, the role of diabetes (Diabetes Care. 2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723; Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020 Jun 11;19(1):76. doi: 10.1186/s12933-020-01047-y), and of hyperglycemia in worse prognosis in COVID-19 (Hyperglycaemia on admission to hospital and COVID-19. Diabetologia. 2020 Jul 6:1-2. doi: 10.1007/s00125-020-05216-2; Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005) has just been previously discussed and published. However, you cannot avoid to discuss these studies. Again, in critical patients there could be an association between ABO group and clinical outcomes (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Indeed, non-0 covid-19 hypertensive patients have significantly higher values of pro-thrombotic indexes, as well as higher rate of cardiac injury and deaths compared to 0 patients (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Moreover, AB0 blood type influences worse prognosis in critical patients with covid-19 infection (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). What is your opinion? Hos is AB0 group represented in your study? In my opinion this information has to be updated in the text. METHODS: How did you collect clinical data? How did you perform diagnosis of SARS/COV2? Can you include a subchapter? Please indicate how many physicians performed imaging, and the modality to perform the exams. Were they blinded to study cohorts and study protocol or not? Please discuss it. How did you calculate sample size of study population? In Methods report a full descriptive sub-chapter about the laboratory diagnosis of COVID-19 infection. Report in detail study population, inclusion vs. exclusion criteria. Did you use lung echography in study population? Please discuss it.

	Include date of start and date of end of study. Include follow-up duration of the study. How did you diagnose and monitor study endpoints? Please discuss it, including all techniques and methods for measuring the study outcomes. RESULTS: In table 1 include a column with “overall study population” characteristics. In table 1 include full medical therapy in study cohorts, and the anti-diabetics medications, and the anti-hyperglycemics drugs used. In the table include the full medical anti-diabetic medication. The table 1 and 2 could be table 1. Please correct it. Again, I would like to see data about study population divided in hospital admitted patients and cases as middle, moderate, severe and critical, and for all this cohort the number of cases under tolicizumab (TCZ) therapy. Indeed, we could speculate that TCZ effects could be reduced by risk factors and metabolic distress (Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005). Could you report the percentage of patients as middle, moderate, severe and critical for each group of study? DISCUSSION: It is too long and not well focused on main study results. Please short it and focus it on main study news. Please re-write it as “what is new and what is known”. In addition, Improve English quality of the text. Include a study flow chart figure.

REVIEWER	Mahmoud, Ibrahim University of Sharjah College of Medicine
REVIEW RETURNED	17-Apr-2021

GENERAL COMMENTS	In this manuscript risk factors for severe outcomes in people with diabetes hospitalized for COVID-19 are described. Major: - The study was time to event (death or discharge) analysis, why authors did not use survival analysis including Kaplan-Meier statistic and Cox regression instead of logistic regression? - Testing logistic regression assumptions need to be highlighted under the statistical analysis section - To improve the external validity of the study it would be worthwhile to describe in more detail the study population: ethnicities, socioeconomic status, catchment area of hospital, has there been a power calculation beforehand? - It is well known that viral infections in people with diabetes increased the risk of diabetic ketoacidosis (DKA) and affect the outcome, why authors did not assess as an event or complication? - Several studies showed that patients with any smoking history are vulnerable to severe COVID-19 and worse in-hospital outcomes, therefore it is essential to adjust for smoking status, why authors did not assess? Minor:

	- In abstract, CKD abbreviation need to be written in full first time. - In line 18 of methods there is a typo error for the HbA1c value.

REVIEWER	Al-Salameh, Abdallah CHU Amiens-Picardie, Endocrinology, Diabetes Mellitus and Nutrition
REVIEW RETURNED	17-Apr-2021

GENERAL COMMENTS	Dear Sir, I read with interest the manuscript by Ortega et al. In this study the authors try to assess risk factors associated with severe outcome (a composite of death or invasive mechanical ventilation) in patients hospitalized with covid-19. They analyze the data according to the presence of hyperglycemia/diabetes or not. They found that the hyperglycemia group had a greater burden of risk factors, more severe profile on admission and more frequent occurrence of almost all endpoints. The study is well written; it does not present new data but adds to already existent data concerning the association between diabetes and severe outcome in patients hospitalized with covid-19. Main issues: - The authors defined the diabetic group as those with known diabetes, those with A1C≥6.5% or blood glucose≥200 mg/dl, and those treated with insulin in the first 24 hours after admission. An important issue is that this definition confounds already known diabetes, newly diagnosed diabetes and stress hyperglycemia. Newly diagnosed diabetes may be associated with a higher risk of severe outcome than known diabetes in the settings of covid-19. So the authors should report the numbers of patients with known diabetes and those with A1C≥6.5% (reflecting a preexistent diabetes) as well as those with blood glucose≥200 mg/dl or insulin use in the first 24 hours after admission (reflecting a newly diagnosed diabetes or stress hyperglycemia). - I have a real problem with the analysis of the association between study endpoints and blood glucose levels on admission. If we look at the supplementary figure 4 we can see that only few patients had blood glucose > 400 mg/dl so it is difficult to draw conclusions about this subgroup. This is reflected by a high variability of the predicted probability of death and the composite endpoint. For example, as per the supplementary figure 5 if somebody had blood glucose of 600 mg/dl his risk of death is somehow between 12% and 80%. Moreover, usually OR for continuous variables such as blood glucose reflects the relative risk per 1 unit increase in the variable level (although there is no reference category), how can the authors explain the OR of death for blood glucose 29.254 for a clinician like me? I think that the authors should present the distribution of blood glucose values and should consider categorization of these values. - I do not think that we can speak of predictor in cross-sectional studies. I'd rather suggest that the authors replace "predict" and "predictor" with "associated with" Minor issues Abstract: Page3, line 16: CKD => chronic kidney disease Introduction:

	Page 5, lines 14-16 “The most prevalent comorbidities associated with increased COVID-19-related morbidity and mortality are the presence of diabetes, cardiovascular diseases (CVDs), chronic lung and kidney disease, hypertension, cancer, obesity, and DM” please delete DM as it is already mentioned. Page 6, line 1, please replace “chance” to “risk” Methods: Page 7, lines 17-19 “4) had a glycosylated hemoglobin (HbA1c) value ≥6.5% (48 mmol/mol) or baseline blood glucose (BG) values ≥200 mg/dL (11.1 mmol/L).” at which time? In the emergency room? Within 24h from admission? … Page 8, lines 4-6 “and concomitant medications (i.e., baseline insulins, systemic corticosteroids, antimicrobials, anticoagulants and antiplatelet agents, and antihypertensive and lipid-lowering drugs)” what about antidiabetic drugs? Results: Page 10, lines 1-7 It seems that death was the most frequent endpoint in the study and that most deaths occurred outside the ICU. Could you please elaborate on this? Page 10, lines 12-13 “only admission to ICU was significantly more frequent among female subjects with DM” form the supplementary figure 2 it seems that ICU admission was more frequent in men! Discussion: Page 13, lines 9-11 “Different meta-analyses have reported that higher mean age and male sex among infected with SARS-CoV-2 are associated with a more severe infection and higher fatality than those with the non-severe disease” this phrase needs to be reformulated Page 13, line 24 “progressive” does that mean “greater or higher”? Page 14, line 20 “we used splines as a scientific and preferable alternative to the categorization of BG levels” please add a reference Page 15, lines 19-20 “missing values could have reduced the statistical power of the study or produced biased estimates” from the supplementary table 2 we can conclude the there was no missing values for all the variables included in the model, please confirm Table 1: how do you explain that only 10% of patients with diabetes were obese? This is not compatible with data about the prevalence of obesity in the general population and in the diabetic population in Spain The supplementary table 3 needs a little bit of organization. Please order the laboratory measurement by system (for example, liver function test should be presented together, complete blood count, inflammatory markers….)

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Dr. Raffaele Marfella , University of Campania
INTRODUCTION:

1. Please introduce the role of ACE2 receptors in SARS/COV2 infection and in the genesis of COVID-19. In this context, as example the hypertensive patients are higher risk patients for COVID19, ICU admission and deaths (Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from centers of southern Italy. J Am Heart Assoc. 2020 Jul 7:e016948. doi: 10.1161/JAHA.120.016948). Please explain this point.
Following the Reviewer's suggestion, we have added a paragraph to introduce the role of the ACE-2 receptor and TMPRSS2 in the pathogenesis of COVID-19 infection. Regarding ACE inhibitors, we have used a very recent meta-analysis of 52 studies (which includes the one the Reviewer mentions) to briefly describe current knowledge on this topic (Page 4, line23):
"SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE-2) as a cellular entry receptor, and the spike protein of the virus needs to be cleaved by cellular proteases (specifically TMPRSS2) to fuse with the cellular membrane [10]. Although it was initially assumed that ACE inhibitors and angiotensin receptor blockers (ARBs) medications might exacerbate COVID-19 infection and lead to worse outcomes, the most recent available meta-analysis did not confirm this higher risk [11]. Finally, it has been suggested that modulating TMPRSS2 expression through specific antibodies or non-coding-RNAs could prevent virus entry into host cells [11, 12], but these potential therapeutic options are still under investigation."
References:
10. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-280.e8. doi:10.1016/j.cell.2020.02.052
11. Baral R, Tsampasian V, Debski M, et al. Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19. JAMA Netw Open 2021;4:e213594. doi:10.1001/jamanetworkopen.2021.3594
12. Matarese A, Gambardella J, Sardu C, et al. miR-98 Regulates TMPRSS2 Expression in Human Endothelial Cells: Key Implications for COVID-19. Biomedicines 2020;8:462. doi:10.3390/biomedicines8110462
2. Again, in the pathogenesis of SARS/COV2 infection, not only the ACE2 receptor but also the serin proteasis expression (TMPRSS2) is another relevant point to discuss. Indeed, as reported by authors, its expression in humans' cells can cause the entrance and replication of SARS/COV2 (miR-98 Regulates TMPRSS2 Expression in Human Endothelial Cells: Key Implications for COVID-19. Biomedicines. 2020 Oct 30;8(11):462. doi: 10.3390/biomedicines8110462). Please describe this point and refer to the suggested reference. In my opinion these informations could improve the Introduction of your article.
Please, refer to our previous response to question #1, where we included a new paragraph on the pathogenesis of COVID-19, introducing the role of TMPRSS2. As suggested by the Reviewer, we have referenced the work of Matarese et al., on the role of a specific mi-RNA that regulates TMPRSS2 as a potential therapeutic target. However, we did not go into detail, as this and other therapeutic options are still being investigated, and because the main target audience of the manuscript are clinicians and epidemiologists who do not necessarily possess great knowledge of molecular genetics.
3. According to authors, I would suggest to introduce the chronic hyperglycemic condition (and insulin resistance), as in the case of diabetes mellitus (Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care. 2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723; Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020 Jun 11;19(1):76. doi: 10.1186/s12933-020-01047-y), but also the hospital admission hyperglycemia as a condition that increases the risk of mortality (Hyperglycaemia on admission to hospital and COVID-19. Diabetologia. 2020 Jul 6:1-2. doi: 10.1007/s00125-020-05216-2; Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005). However, please describe in detail this point. Refer to the suggested reference.

We agree with the Reviewer that hyperglycaemia in the context of COVID-19 deserves attention in the Introduction section of the manuscript. Following this advice, we have included a paragraph to introduce the association of this condition with bad prognosis and negative impact in the therapeutic response to tocilizumab. As references, we have included two recent meta-analyses (already including the 2 references from Sardu et al., suggested by the Reviewer) and the Marfella study on tocilizumab. The new paragraph reads as follows (Page 5, line18):
“Early reports showed that about half of patients with severe COVID-19 presented acute hyperglycaemia, with no more than 10% of them having a prior diagnosis of DM [22, 23]. Following these observations, two meta-analyses concluded that hyperglycaemia at hospital admission is associated with severe complications and mortality, regardless of diabetes status [24,25]. Moreover, hyperglycaemia also has a negative impact on the therapeutic response to tocilizumab in patients with COVID-19-related systemic inflammation [26].
References:
22. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.

23. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146:110-8.

24. Lee MH, Wong C, Ng CH, Yuen DCW, Lim AYL, Khoo CM. Effects of hyperglycaemia on complications of COVID-19: A meta-analysis of observational studies. Diabetes Obes Metab 2021;23:287-9.

25. Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep 2021;41.

26. Marfella R, Paolisso P, Sardu C, et al. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes Metab 2020;46:403-5.
4. However, as you could see in the current international literature, the role of diabetes (Diabetes Care. 2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723; Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol. 2020 Jun 11;19(1):76. doi: 10.1186/s12933-020-01047-y), and of hyperglycemia in worse prognosis in COVID-19 (Hyperglycaemia on admission to hospital and COVID-19. Diabetologia. 2020 Jul 6:1-2. doi: 10.1007/s00125-020-05216-2; Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005) has just been previously discussed and published. However, you cannot avoid to discuss these studies.
Please, see our previous response, as we understand that this question is almost identical to question #3 and that the lack of information on hyperglycaemia and COVID-19 prognosis has been addressed in our response to question #3.
5. Again, in critical patients there could be an association between ABO group and clinical outcomes (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Indeed, non-0 covid-19 hypertensive patients have significantly higher values of pro-thrombotic indexes, as well as higher rate of cardiac injury and deaths compared to 0 patients (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi: 10.1186/s12872-020-01658-z). Moreover, AB0 blood type influences worse prognosis in critical patients with covid-19 infection (Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord. 2020 Aug 14;20(1):373. doi:

10.1186/s12872-020-01658-z). What is your opinion? Hos is AB0 group represented in your study? In my opinion this information has to be updated in the text.
As suggested by the Reviewer, we have added a paragraph to briefly discuss the role of the AB0 blood type in selected groups of patients. Regarding the Reviewer's question on the distribution of AB0 phenotypes in our study, unfortunately, we did not have access to this variable in the database we used, so it could not be analysed.
The new paragraph reads as follows (Page 4, line 18):
"In addition, the AB0 blood type may play a role in the susceptibility and severity of COVID-19 infection, which could be of importance in patients with underlying high-risk conditions[8]. For instance, it has been reported that non-0 blood group hypertensive patients have significantly higher values of pro-thrombotic indexes and increased rates of cardiac injury and deaths compared with 0 patients[9]."
References:
8. Pendu J Le, Breiman A, Rocher J, et al. ABO Blood Types and COVID-19: Spurious, Anecdotal, or Truly Important Relationships? A Reasoned Review of Available Data. Viruses 2021;13:160. doi:10.3390/v13020160

9. Sardu C, Marfella R, Maggi P, et al. Implications of AB0 blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord 2020;20:373. doi:10.1186/s12872-020-01658-z

METHODS:
6. How did you collect clinical data?
Data were obtained from pseudonymized electronic health records provided by six general hospitals from the HM Hospitales group (Spain). This group of hospitals, in order to promote COVID-19 related research, created a project/platform called "Covid Data Save Lives" with the aim of sharing clinical information already collected by the medical staff during the first COVID-19 wave. All the information related to the collection and description of the clinical data is available on the hospital web-page. A formal petition with specific study protocol and ethics committee approval was obtained before access to the database was granted.
To address this point, we modified the Study design and settings subsection in the Methodology section of the manuscript (Page7, line 12):
"(…) The study data were collected by medical professionals of the HM Hospitales group (Spain) during the first wave of the COVID-19 pandemic. In order to promote COVID-19 related research, the HM Hospitales group pseudonymized the medical history of SARS-CoV-2 infected patients and created a project titled: "Covid Data Save Lives". Before access was granted, a formal petition, specific study protocol, and ethics committee approval were obtained.
Additionally, in the Online Supplementary material of the manuscript (Database description section), we now provide the link to the official project web-page, which contains information on the database and describes data collection and the variables available (https://www.hmhospitales.com/coronavirus/covid-data-save-lives/english-version).
7. How did you perform diagnosis of SARS/COV2? Can you include a subchapter?
According to the database, the diagnosis of COVID-19 was made microbiologically by proven SARS-CoV-2 infection (COVID POSITIVE variable) by reverse transcription-polymerase chain reaction (RT-PCR). Unfortunately, no further information is available on the specific name of the kit provider or technique in the database.
8. Please indicate how many physicians performed imaging, and the modality to perform the exams. Were they blinded to study cohorts and study protocol or not? Please discuss it.
According to the official web page from HM Hospitales, the radiology/radiodiagnosis or diagnostic imaging departments have in total 143 medical doctors working in different hospitals of this group. Regarding the

blinding of the study cohorts, we cannot confirm this as the data was anonymized and no information on this issue was available in the dataset description.

9. How did you calculate sample size of study population?

Data from our study are part of the program “Covid Data Save lives”, where HM Hospitales created an anonymous dataset freely available to the international medical and scientific community with all the available clinical information on patients treated at their hospital centres for the SARS-CoV-2 virus. We analysed the entire population and no specific sample size was calculated.

10. In Methods report a full descriptive sub-chapter about the laboratory diagnosis of COVID-19 infection. Report in detail study population, inclusion vs. exclusion criteria.

As suggested by the Reviewer, we have modified the Inclusion and Exclusion Criteria section of the manuscript to include further details (Page 7, line 20):

“(…) The study enrolled people over 18 years of age with SARS-CoV-2 infection (COVID positive) microbiologically proven by reverse transcription polymerase chain reaction (RT-PCR). Those with DM were identified in the database if they: 1) had any ICD-10 (International Statistical Classification of Diseases) diagnostic code for type 1 or type 2 DM (i.e., E.10 and E11), 2) were on treatment with antidiabetic drugs, 3) had a register of insulin use within the first 24 hours after admission, or 4) had a glycosylated haemoglobin (HbA1c) value ≥6.5% (48 mmol/mol; first available record after admission) or baseline blood glucose (BG) values ≥200 mg/dL (11.1 mmol/L; recorded within the first 24 hours of admission). Subjects with no confirmation of SARS-CoV-2 infection and those younger than 18 years were excluded from the study.

11. Did you use lung echography in study population? Please discuss it.

The data of our study are from the first COVID-19 wave. Unfortunately, at that moment, lung echography was not an imaging technique included in standard hospital protocols.

12. Include date of start and date of end of study. Include follow-up duration of the study.

As suggested by the Reviewer, we have modified the Methods section of the manuscript to provide detailed information on the duration of the study (Page 7, line 5):

“(…) The database included information related during the hospital stay (diagnosis and procedures codes, prescribed medications, vital signs, and laboratory parameters), from 2,310 subjects during the first COVID-19 wave, with a hospital admission between January 27 and April 24, 2020 (study start and end date, respectively). Subjects were followed from admission to hospital discharge or death.

13. How did you diagnose and monitor study endpoints? Please discuss it, including all techniques and methods for measuring the study outcomes.

Following the Reviewer’s suggestion, we have modified the Study variables section of the manuscript to include this information (Page 8, line15):

“(…) We considered the following variables as events or complications during the hospital stay: death, acute respiratory distress syndrome (ARDS), pulmonary thrombosis, neurologic complications, thrombotic complications identified by ICD-10 diagnostic codes, admission to ICU, and invasive mechanical ventilation (IMV) identified by ICD-10 procedure codes. The composite primary outcome was defined as death or IMV.

RESULTS:

14. In table 1 include a column with “overall study population” characteristics.

Following the Reviewer's comment, we have added a column with overall study population characteristics in the Table 1.

15. In table 1 include full medical therapy in study cohorts, and the anti-diabetics medications, and the anti-hyperglycemics drugs used.

Following the Reviewer's advice, pharmacological therapy has been included in the new Table 1.

16. In the table include the full medical anti-diabetic medication. The table 1 and 2 could be table 1. Please correct it.

As suggested by the Reviewer, we have added concomitant medication in table 1. However, and due to the large amount of information, we provide the data on laboratory parameters as Supplementary Table 1.

17. Again, I would like to see data about study population divided in hospital admitted patients and cases as middle, moderate, severe and critical, and for all this cohort the number of cases under tolicizumab (TCZ) therapy. Indeed, we could speculate that TCZ effects could be reduced by risk factors and metabolic distress (Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes and Metabolism 2020; doi: 10.1016/j.diabet.2020.05.005). Could you report the percentage of patients as middle, moderate, severe and critical for each group of study?

Unfortunately, we did not have data on the grade of severity at admission due to the database's characteristics and nature. However, we are now providing data on the use of tocilizumab (TCZ) therapy between groups in Table 1. We observed statistical differences in the use of this drug between two groups of subjects, as it was used almost twice as much among DM patients. We have added these results on the use of biological therapy during the hospital stay (Page 10, line 10):

"(…) Regarding the pharmacological therapy used during the hospital stay, we observed differences and increased use of almost all drugs of interest among DM subjects, compared with non-DM, especially for diuretics, systemic corticosteroids, and tocilizumab."

DISCUSSION:

18. It is too long and not well focused on main study results. Please short it and focus it on main study news. Please re-write it as "what is new and what is known".

Following the Reviewer's advice, we reduced the Discussion section considerably (by more than 400 words). In this new version, we did our best to limit the discussion to the key findings of the study and compare them with existing literature.

19. In addition, Improve English quality of the text.

We regret that there were problems with the English. In response to this comment, the paper has been carefully revised by a professional language editing service to improve the grammar and readability.

20. Include a study flow chart figure.

Following the Reviewer's recommendation, we have moved the flow chart figure (provided as Supplementary Figure in the previous version of the manuscript) to the main text in the new version.

Reviewer #2

Dr. Ibrahim Mahmoud, University of Sharjah College of Medicine

Comments to the Author:

Major comments:

1. The study was time to event (death or discharge) analysis, why authors did not use survival analysis including Kaplan-Meier statistic and Cox regression instead of logistic regression?

We thank the Reviewer for this comment. The study only analysed subjects during their hospital stay, and a relatively short period of observation, this corresponds to a cross-sectional design with no different time points available for each variable. Additionally, diagnosis (recording) of the outcomes during the hospital stay is often not at the time of occurrence which was the case in this database. Further, we understand that the inclusion of data on hospitalization episodes ought to be considered as a cross-sectional design. Therefore, we used logistic regression analysis to explore the association between mortality and mortality or mechanical ventilation and independent variables.

2. Testing logistic regression assumptions need to be highlighted under the statistical analysis section

We have made the changes suggested by the Reviewer in the statistical analysis section, highlighting the different models used in testing logistic regression assumptions with main study outcomes. Moreover, these models are confirmatory of hypotheses with adjustment of clinically relevant variables. Model

assumes the linearity of the predictors on logit of each outcome. Additionally, we have evaluated goodness of fit with test H&L test (Hosmer-Lemeshow test) and applied this test, to all models. The Hosmer–Lemeshow test is a statistical test for goodness of fit for logistic regression models. Like most goodness of fit tests, the small p-values (usually under 5%) mean that model is not a good fit. However, in our case all of the models had p-values >0.05(Page 9, line 3):
"(…) In addition, several models of interest were tested (a model with basic clinical variables such as age and sex, a model adding obesity, hypertension and hyperlipidaemia, and a model adding organ lesion variables, such as CVD, heart failure, CKD, COPD), namely with the sequential inclusion of different covariates and the estimated differences expressed as odds ratio (OR) and their respective 95% confidence intervals (CI). We evaluated goodness of fit of the logistic regression models with H&L test (Hosmer–Lemeshow test).
We also added the value for Hosmer–Lemeshow test in the Supplementary Table 3.

3. To improve the external validity of the study it would be worthwhile to describe in more detail the study population: ethnicities, socioeconomic status, catchment area of hospital, has there been a power calculation beforehand?
We thank the Reviewer for the comment. This database is a part of the program "Covid Data Save lives", where the HM Hospitales group created an anonymous dataset freely available to the international medical and scientific community with all the clinical information available on patients treated at their hospital centres for the SARS-CoV-2 virus. We analysed the entire database available with all cases available at that moment, so no statistical power was calculated. Unfortunately, no information on ethnicity, socioeconomic status or area of the hospital was available. We did changes in the Statistical analysis section, (page 9, line 12)
"(…)We analysed the entire database available and no statistical power was calculated."
4. It is well known that viral infections in people with diabetes increased the risk of diabetic ketoacidosis (DKA) and affect the outcome, why authors did not assess as an event or complication?
We thank the Reviewer for the comment. Unfortunately, the diagnostic code for diabetic ketoacidosis was not available from the database, therefore it was not possible to include this event in the analyses.
5. Several studies showed that patients with any smoking history are vulnerable to severe COVID-19 and worse in-hospital outcomes, therefore it is essential to adjust for smoking status, why authors did not assess?
As we mentioned before, this database was a part of the program "Covid Data Save lives", with the purpose of analysing the clinical variables of patients admitted to HM Hospitales during the first wave of the COVID-19 pandemic. No data on smoking status, toxic habits or socio-demographic variables were available. Since we understand that this is a limitation of the study, we have accordingly modified the Limitations section of the manuscript (Page 15, line 5):
"(…) Moreover, data on socio-demographic characteristics (ethnicity, race, economic or educational status) and toxic habits (smoking, alcohol or drug use) were not available. "
Minor comments:

6. In abstract, CKD abbreviation need to be written in full first time.
Thank you for spotting this mistake. It has been corrected in the new version of the manuscript.
7. -In line 18 of methods there is a typo error for the HbA1c value.
Thank you for spotting this typo. It has been corrected in the new version of the manuscript.

Reviewer #3
Dr. Abdallah Al-Salameh, CHU Amiens-Picardie
Main issues:

1. The authors defined the diabetic group as those with known diabetes, those with A1C≥6.5% or blood glucose≥200 mg/dl, and those treated with insulin in the first 24 hours after admission. An important issue is that this definition confounds already known diabetes, newly diagnosed diabetes and stress hyperglycemia. Newly diagnosed diabetes may be associated with a higher risk of severe outcome than known diabetes in the settings of covid-19. So the authors should report the numbers of patients with known diabetes and those with A1C≥6.5% (reflecting a preexistent diabetes) as well as those with blood glucose≥200 mg/dl or insulin use in the first 24 hours after admission (reflecting a newly diagnosed diabetes or stress hyperglycemia).

We thank the Reviewer for this comment. We separately calculated different definitions of diabetic group subjects and performed the analysis for study events. The descriptive table of the events for the two groups are presented in Supplementary Table 2. Additionally, we mentioned the results of this suggestion in the Results section (Page 11, line 4)
"(…) Within the diabetes group, when we stratified by pre-existing DM (DM codes and/or HbA1c ≥6.5% and/or antidiabetic treatment) and "stress" hyperglycaemia/ unknown diabetes (glucose ≥200 mg/dL or insulin use within the first 24h period after admission), we observed higher percentages for death, death or IMV, ARDS, admission to ICU and IMV events in subjects with "stress" hyperglycaemia. The results of this stratification are presented in Supplementary Table 2.
Supplementary table 2. Number of events in patients with pre-existing diabetes and stress hyperglycaemia

2. I have a real problem with the analysis of the association between study endpoints and blood glucose levels on admission. If we look at the supplementary figure 4 we can see that only few patients had blood glucose > 400 mg/dl so it is difficult to draw conclusions about this subgroup. This is reflected by a high variability of the predicted probability of death and the composite endpoint. For example, as per the supplementary figure 5 if somebody had blood glucose of 600 mg/dl his risk of death is somehow between 12% and 80%. Moreover, usually OR for continuous variables such as blood glucose reflects the relative risk per 1 unit increase in the variable level (although there is no reference category), how can the authors explain the OR of death for blood glucose 29.254 for a clinician like me?
I think that the authors should present the distribution of blood glucose values and should consider categorization of these values.

We used an adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves to explore the association between study outcomes and blood glucose. The "s(Glucose)" term in Supplementary Table 7 refers to the spline, and as you may note, there is no coefficient because it just represents a nonlinear function, and its shape can be seen in Figures 5 and 6. Therefore, there is no clinical interpretation for this coefficient. To avoid potential for misunderstanding among readers, we have removed the value from Supplementary Table 7.
3. I do not think that we can speak of predictor in cross-sectional studies. I'd rather suggest that the authors replace "predict" and "predictor" with "associated with"

The Reviewer is right that “predictor” is not an adequate term in the context of a cross-sectional study. The manuscript has been revised and this term has been changed to “associated with” where applicable.

Minor issues

4. Abstract: Page3, line 16: CKD => chronic kidney disease
This mistake has been corrected in the new version of the manuscript.
Introduction:

5. Page 5, lines 14-16 “The most prevalent comorbidities associated with increased COVID-19-related morbidity and mortality are the presence of diabetes, cardiovascular diseases (CVDs), chronic lung and kidney disease, hypertension, cancer, obesity, and DM” please delete DM as it is already mentioned.
This repetition has been corrected in the new version of the manuscript.
6. Page 6, line 1, please replace “chance” to “risk”
“Chance” has been replaced by “risk” in the new version of the manuscript.
Methods:

7. Page 7, lines 17-19 “4) had a glycosylated hemoglobin (HbA1c) value ≥6.5% (48 mmol/mol) or baseline blood glucose (BG) values ≥200 mg/dL (11.1 mmol/L).” at which time? In the emergency room? Within 24h from admission? …

The Reviewer is right that this information was lacking in the manuscript. In the new version that we are submitting, we have added that BG values were those recorded within the first 24 hours of admission, and HbA1c values the first available record after admission, as this is not a routine laboratory parameter in the emergency room. The text now reads as follows (Page 8, line 1):
“(...) or 4) had a glycosylated haemoglobin (HbA1c) value ≥6.5% (48 mmol/mol; first available record after admission) or baseline blood glucose (BG) values ≥200 mg/dL (11.1 mmol/L; recorded within the first 24 hours of admission).”

8. Page 8, lines 4-6 “and concomitant medications (i.e., baseline insulins, systemic corticosteroids, antimicrobials, anticoagulants and antiplatelet agents, and antihypertensive and lipid-lowering drugs)” what about antidiabetic drugs?

Following the Reviewer’s suggestions, we have added concomitant medications, and antidiabetic drugs to the Table 1.

Additionally, we have added a description of the pharmacological therapy in the results section: baseline characteristics (Page 10, line 10):

“(...) Regarding the pharmacological therapy used during the hospital stay, we observed differences and increased use of almost all drugs of interest among DM subjects, compared with non-DM, especially for diuretics, systemic corticosteroids, and tocilizumab.

Results:

9. Page 10, lines 1-7 It seems that death was the most frequent endpoint in the study and that most deaths occurred outside the ICU. Could you please elaborate on this?

We thank the Reviewer for this comment; as we have mentioned in the text, “the most frequent outcome was the composite of death or IMV (31% in the DM group vs. 14% in the non-DM group; Figure 1) followed by death (26.3% vs. 11.3%), admission to ICU (21% vs. 6.9%), IMV (10.7% vs. 4.2%), and ARDS (3.8% vs. 1.5%)”. Due to the nature of this database, with a cross-sectional design of the study, we cannot confirm whether the deaths occurred outside the ICU or during the ICU stay.

10. Page 10, lines 12-13 “only admission to ICU was significantly more frequent among female subjects with DM” form the supplementary figure 2 it seems that ICU admission was more frequent in men!

We apologise for this mistake. Supplementary Figure 1 is indeed correct. We have modified the text of the manuscript to describe this finding correctly (Page 11, line 24):
“When stratifying the results by sex, we did not observe differences except for admission to ICU, which was significantly more frequent among male subjects with DM (Supplementary Figure 1).”
Discussion:

11. Page 13, lines 9-11 “Different meta-analyses have reported that higher mean age and male sex among infected with SARS-CoV-2 are associated with a more severe infection and higher fatality than those with the non-severe disease” this phrase needs to be reformulated

This sentence has been rephrased (Page 13, line 8):
“older age and male sex are characteristics associated with severe COVID-19 infection and high fatality rates [17, 30, 31].”
12. Page 13, line 24 “progressive” does that mean “greater or higher”?

We apologise for the vagueness of the sentence. Actually, in that sentence we meant that the worse the renal function (measured as glomerular filtration rate) the higher incidence of adverse COVID-19-related outcomes. To clarify this issue, we have modified this sentence, which now reads as follows (Page 13, paragraph 20):
“Moreover, a recent study conducted in Danish hospital-diagnosed COVID-19 patients reported that kidney insufficiency was independently associated with increased risk of severe disease or death, and the degree of renal impairment inversely correlated with the rate of adverse outcomes.”
13. Page 14, line 20 “we used splines as a scientific and preferable alternative to the categorization of BG levels” please add a reference
We have added the reference from Alahmad et al. (2020): Fasting Blood Glucose and COVID-19 Severity: Nonlinearity Matters. Diabetes Care 2020; 43: 3113–3116.
14. Page 15, lines 19-20 “missing values could have reduced the statistical power of the study or produced biased estimates” from the supplementary table 2 we can conclude the there was no missing values for all the variables included in the model, please confirm

We thank the Reviewer for this comment. The comorbidities variables in our database were categorical (yes/no); thus, the absence of the diagnostic code was considered as No, while the presence as Yes. For the sex variable, there were no missing values.

15. Table 1: how do you explain that only 10% of patients with diabetes were obese? This is not compatible with data about the prevalence of obesity in the general population and in the diabetic population in Spain

This is most probably related to the clinician's under-recording for this particular condition. Firstly, obesity and overweight are frequently omitted in medical records unless severe or associated with additional health problems (e.g., diabetes). Secondly, during the first wave of the pandemic, obesity had not yet been identified as a significant risk factor and, thus, not always registered. Since we understand that this is a limitation of the study, we have added a sentence on this issue (Page 15, line 7):
"Secondly, we had very few registers for some important variables for diabetes, such as Hb1Ac (data from only 36 patients) and no data on weight or BMI. Indeed, no more than 10% of the patients had documented obesity, which is clearly lower than the expected prevalence in the general population. This was most probably related to the clinician's under-recording of this particular condition, and to the fact that, during the first wave, obesity had not yet been identified as a significant risk factor and, thus, not specifically registered."
16. The supplementary table 3 needs a little bit of organization. Please order the laboratory measurement by system (for example, liver function test should be presented together, complete blood count, inflammatory markers….)

We have organized the variables in the Supplementary Table 1 as was suggested by the Reviewer. Thank you for this improvement.

VERSION 2 – REVIEW

REVIEWER	Marfella , Raffaele University of Campania
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Al-Salameh, Abdallah CHU Amiens-Picardie, Endocrinology, Diabetes Mellitus and Nutrition
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	I would like the authors for their work. The manuscript is now acceptable for publication. I have one remaining question and two minor comments: Question: less than 40% of patients with diabetes (approximately 60% of those with known diabetes) were treated for diabetes! Is it right? Is there any underreporting? Comment: - page 8, line 16: neurological complications need to be defined. - page 11, line 13: it is about Figure 3 and Supplementary Table 3 and not (Figure 2; Supplementary Table 2)

VERSION 2 – AUTHOR RESPONSE

Reviewer #3

Dr. Abdallah Al-Salameh, CHU Amiens-Picardie

Main comment:

1. I would like the authors for their work. The manuscript is now acceptable for publication. I have one remaining question and two minor comments:

Question: less than 40% of patients with diabetes (approximately 60% of those with known diabetes) were treated for diabetes! Is it right? Is there any underreporting?

We thank the Reviewer for this comment. Indeed, the underreporting of health conditions previous to hospital admission such as diabetes was one of the limitations of this hospital database. To circumvent this issue, we used a proxy algorithm to identify subjects with diabetes, as described in the Inclusion and Exclusion Criteria subsection of the manuscript (Page 7-8; lines 20-24 and 1-3, respectively). Moreover, as pointed by the Reviewer, the proportion of patients identified as having diabetes and receiving glucose-lowering treatment at hospital admission was low. Since we had no data on the patient's treatments prior to admission, this most probably indicates underreporting. As we understand that this is an additional database limitation, we have added a sentence in the Discussion section of the manuscript (page 15, lines 15-18):

"Besides, we had no access to the patient's treatments prior to hospital admission. Since the proportion of patients identified as having diabetes and receiving glucose-lowering agents was surprisingly low (approximately 40%), this can also be attributed to antidiabetic treatment underreporting at admission."

2. Comment:

- page 8, line 16: neurological complications need to be defined.

As suggested by the Reviewer, we included the list of neurologic and thrombotic complications considered as events or complications during the hospital stay in the Study variables section of the manuscript (Page 8, line 17-18):

"(…) neurologic complications (including encephalopathy, encephalitis, myelitis, and encephalomyelitis), thrombotic complications (i.e., phlebitis and thrombophlebitis) identified by ICD-10 diagnostic codes, (…)"

- page 11, line 13: it is about Figure 3 and Supplementary Table 3 and not (Figure 2; Supplementary Table 2)

This typo has been corrected in the new version of the Results section of the manuscript (Page 11, line16):