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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19

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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19

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Abstract:

Aim: This study's objective was to assess the risk of severe in-hospital complications of patients admitted for coronavirus disease (COVID-19) and diabetes mellitus (DM).

Design: This was a cross-sectional study

Settings: We used pseudonymised medical records data provided by six general hospitals from the HM Hospitales group in Spain.

Outcome measures: Multiple logistic regression analyses were used to identify predictors of mortality and the composite of mortality or invasive mechanical ventilation (IVM) in the overall population and stratified for the presence or absence of DM. Spline analysis was conducted in the whole population to investigate the relationship between glucose levels at admission and outcomes**.**

Results: Overall, 1,621 individuals without DM and 448 with DM were identified in the database. The persons with DM were on average 5.1 years older than those without. The overall in-hospital mortality was 18.6% (N=301) and was higher among patients with DM than without (26.3% vs 11.3%; p<0.001). DM was an independent predictor of death and death or IVM (OR=2.33, 95% CI: 1.7–3.1 and OR=2.11, 95% CI: 1.6– 2.8, respectively; p<0.001). In subjects with DM, the only variables independently predicting both outcomes were age >65 years, male gender, and pre-existing CKD. We observed a non-linear relationship between blood glucose levels at admission and the risk of in-hospital mortality and death or IVM. The highest predicted probability for each outcome (near 50%) was at random glucose of around 550 mg/dL (30.6 mmol/L), and the risks flattened above this value.

Conclusion: The results confirm the high burden associated with DM in patients hospitalised with COVID-19 infection, particularly among males, the elderly, and those with impaired kidney function. Moreover, hyperglycaemia on admission is a strong predictor of poor outcomes,

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suggesting that its optimisation in a personalised manner could help to improve the outcomes during the hospital stay.

Keywords: COVID-19, Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation

Strengths and limitations of this study

- A major strength of our study is the thorough methodological approach to analyse the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia.
- We were limited by not having access to the patient's medical history prior to admission and few registers for some important variables for diabetes (such as Hb1Ac) and no data on weight or BMI (only the presence of obesity).
- The selection of subjects with DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose levels at admission.
- We used random blood glucose on admission for the spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.

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1. Introduction

On the 30th January 2020, the World Health Organization (WHO) declared the outbreak of the novel SARS-CoV-2 coronavirus a public health emergency of international importance. A few days later, the respiratory disease caused by SARS-CoV-2 was officially named COVID-19 (Corona Virus Infectious Disease 2019) [1, 2]. The first positive diagnosed person in Spain was confirmed on 31st January 2020, in the island of La Gomera [3]. The median age of hospitalised patients infected with SARS-CoV-2 is 46.2 years, men comprise about 60%, and the average incubation period is 5.7 days [4]. As of 8th February 2021, approximately 3 million persons have been infected with SARS-CoV-2 in Spain since the start of the COVID-19 pandemic, and 62,295 persons have died.

Several meta-analyses have reported that the most severe and fatal cases of COVID-19 occur among the elderly and in patients with underlying comorbidities [5-7]. Indeed, those with two or more concomitant diseases have a significantly higher risk of admission to an intensive care unit (ICU), invasive ventilation, or death compared to those with a single concomitant disease or without comorbidities [8]. 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 [5-7].

Previous studies have reported that people with DM are prone to new infections and recurrence, particularly influenza and pneumonia, due to impaired defences and disease complications [8-11]. Although the estimated prevalence of DM in COVID-19 infected patients varies greatly by geographical region, it is considered similar to DM prevalence in the general population, thus not representing a risk factor for infection [12]. However, the prevalence of diabetes among COVID-19 hospitalised subjects is higher than the overall diabetes prevalence [12, 13]. A study conducted in England found that a third of in-hospital deaths occurred in people with type 2 DM and that these patients had greater odds of COVID-19-related in-hospital death than those without DM [14]. This observation has been confirmed in a meta-analysis showing that DM is

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associated with a 2-fold higher chance of dying from COVID-19 [15], and a second one reporting that patients with pre-existing DM have a 3-fold greater risk of in-hospital mortality [16].

In Spain, DM is a highly prevalent disease in people over 18 years of age (13.8% of the population) [17]. Given the high prevalence of DM and the additional challenging scenario that COVID-19 poses to the health care professionals in this particular population, it is crucial to accumulate and share information and data from different countries and regions [18]. Following this notion, the main objective of this study was to assess the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia at admission in Spain.

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2. Methods

2.1 Study design and settings

This was a cross-sectional study in hospitalized individuals infected with SARS-CoV-2, stratified by presence or absence of DM. Data were obtained from pseudonymized electronic health records provided by six general hospitals from HM Hospitales group (Spain). The database included retrospective information related to, medical history (prior admissions, diagnoses and treatment) and current admission data (procedures' codes, prescribed medications, vital signs, and laboratory parameters) from 2,310 subjects with a hospital admission between the 27th January 2020 and the 24th April 2020. Subjects were followed from admission to hospital discharge or death.

The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol, Barcelona (approval number: 20/089-PCV).

2.2 Inclusion and Exclusion Criteria

The study enrolled people older than 18 years with microbiologically proven SARS-CoV-2 infection 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 in the first 24 hours since admission, or 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).

2.3 Study Variables

The following baseline variables were collected: age and sex; SARS-CoV-2 diagnosis (positive RT-PCR); comorbidities (i.e., hypertension, hyperlipidaemia, obesity [BMI ≥30 kg/m^2], CVD, heart failure, cerebrovascular diseases, ischemic heart disease, chronic renal disease, chronic obstructive

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pulmonary disease [COPD], asthma, mental disorders, and cancer); blood laboratory parameters (i.e., HbA_{1c}, BG, electrolytes, renal function, liver function, haematology and coagulation, inflammation markers, and gas tests); clinical parameters (i.e., systolic and diastolic blood pressure, heart rate, and temperature), and concomitant medications (i.e., baseline insulins, systemic corticosteroids, antimicrobials, anticoagulants and antiplatelet agents, and antihypertensive and lipid-lowering drugs).

As events or complications during hospital stay, we considered the following variables: death, acute respiratory distress syndrome (ARDS), pulmonary thrombosis, neurologic complications, thrombotic complications, admission to ICU, and invasive mechanical ventilation (IMV). The composite primary outcome was defined as death or IMV.

2.4 Statistical Methods

The demographic and clinical characteristics of the two groups of hospitalized patients (i.e., with or without DM) were compared and summarized at the quantitative (minimum, maximum, median, first and third quartile, mean, and standard deviation (±SD) or categorical level (frequency, number and %).

The association between the study outcomes (i.e., mortality and mortality or mechanical ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and associated risk factors. Several models of interest were tested, namely with the sequential inclusion of different covariates and the estimated differences expressed as odds ratio (OR) and their respective 95% confidence intervals (CI). To analyse the nonlinear relationship of random blood glucose levels on admission with the two study outcomes, we used an adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves with two degrees of freedom (knots) using the mgcv package in R, version 1.8-31[19] with adjustment for potential

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confounders. Data management and statistical analyses were performed using the R statistical software version 3.6.1 (https://www.r-project.org/).

2.5 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

3.1. Baseline Characteristics

Out of the 2,306 subjects admitted to hospital within the timelines, 2,069 were older than 18 years and had a positive diagnostic test for SARS-CoV-2 (**Supplementary Figure 1**). Among them, 448 (21.7%) were identified as having DM and 1,621(78.3%) without DM (non-DM group). The characteristics of the two populations at hospital admision are shown in **Table 1**. Subjects with DM were on average 5.1 years older than those in the non-DM group and more frequently male (67.9% *vs.* 58.6%). Moreover, individuals in the DM group had a poor comorbidity profile, with higher frequency of all assessed prior conditions except for cerebrovascular diseases and asthma.

Regarding laboratory parameters on admission (**Supplementary Table 1)**, the DM group had slightly lower estimated glomerular filtration rates (eGFR) (73.5±26.5 mL/min/1.73 m^2 *vs.* 81.2±23.9 mL/min/1.73 m^2; p<0.001) and higher levels of serum creatinine (1.09±0.72 mg/dL *vs.* 0.94±0.51 mg/dL; p<0.001) than the non-DM group. Regarding markers of inflammation and infection, we observed higher levels of C-reactive protein and procalcitonin in the DM group (97.1±107 mg/L *vs.* 75.9± 82.5 mg/L and 0.66±1.30 mg/L *vs.* 0.39±1.30 mg/L, respectively; p<0.001). We also oberved higher levels of D-dimer, a marker of endothelial and coagulation dysfunction in the DM group (3990 ±10800 ng/mL *vs* .2340 ±6720 ng/mL, respectively).

3.2 Events and complications during in-hospital stay

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A total of 301 (14.5%) subjects positive for SARS-CoV-2 had in-hopsital death, 118 (26.3%) out of 448 in the DM group and 183 (11.3%) out of 1621 in the non-DM group (p<0.001; **Figure 1**). All studied events, except pulmonary embolism and thrombotic or neurologic complications, were significantly more frequent among patients with than without DM (**Figure 1**). 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%).

The frequency of events by group and age showed that, in both subjects with and without DM, death and the composite of death or IMV were significantly more frequent among those >65 years (**Supplementary Figure 2**). In contrast, the proportion of subjects needing IVM and ICU admission was significantly higher among those ≤65 years and DM, while age did not make any difference for those without DM. When stratifying the results by gender, only admission to ICU was significantly more frequent among female subjects with DM, while for all the other outcomes, we did not observe gender differences (**Supplementary Figure 1**).

3.3. Baseline demographic and clinical characteristics predicting in-hospital death and death or IMV

For the overall hospitalised population, the demographic characteristics that significantly predicted mortality were male sex and older age (OR=1.98, 95% CI=1.2–3.3 and OR=1.10, 95% CI=1.08– 1.11, respectively) (**Figure 2; Supplementary Table 2**). The comorbidities independently associated with increased odds of death were DM (OR=2.33, 95% CI=1.7–3.1), CKD (OR=2.14, 95% CI=1.2–3.7), and COPD (OR=1.72, 95% CI=1.1–2.8).

When considering the composite outcome of death or IMV, the same variables that predicted death (i.e., age, sex, diabetes, CKD, and COPD) were identified as increasing the risk. In additon, obesity emerged as an independent predictor (OR=1.98, 95% CI=1.5–2.7) (**Figure 2**, **Supplementary Table 2).**

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The multiple logistic regression models were repeated to rule out the potential interaction of DM with different clinical conditions (i.e., obesity, hyperlipidemia, obesity and hyperlipidemia, HF, CKD, and COPD) for the in-hospital death outcome. The results showed none of these conditions affected the relationship between the risk of death and DM (**Supplementary Table 3**).

3.4. Factors predicting hospital death and death or IMV by comorbid diabetes

A sub-analysis was done separately for subjects with or without DM. In the DM subgroup, the only variables independently predicting the risk of both mortality and death or IVM were male sex, older age, and CKD (**Figure 3A** and **Supplementary Table 4** and **5**). In contrast, in subjects without DM, besides the above variables, the odds of death were also increased among subjects with CVD (OR=1.94, 95% CI=1.03– 3.7), and the odds of death or IVM among those with obesity or COPD (OR=2.96, 95% CI=1.7–5.3 and OR=2.30, 95% CI= 1.4 – 3.8, respectively) (**Figure 3B** and **Supplementary Table 4** and **5)**.

3.5. Factors predicting hospital death and death or IMV by glucose levels at admission

We used non-parametric logistic regression models to assess whether there was a relationship between random BG on admission and the risk of mortality (and death or IMV). We observed a marked non-linearity in the effect of BG on admission in the risk of both outcomes (**Figure 4A and 4B** and **Supplementary Table 6**). While the risk was increased among subjects with high random BG levels on admission, the magnitudes of the predicted mortality differed depending on the baseline values, with a large increase in the log-odds of death or IVM with values up to 200 mg/dL (11.1 mmol/L) and smaller increases above this level. The prediction models (**Figure 5A and 5B**) showed that the highest predicted probability of death (near 50%) was at around 550 mg/dL (30.6 mmol/L) and, above this value, the mortality risk flattened.Finally, the multivariate model showed that beside glucose at admission male sex, older age, CKD, and COPD were predictive of in-

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hospital death (**Supplementary Table 6**). These variables were predictors of death or IMV too, but obesity was an additional risk factor (**Supplementary Table 6**).

4. Discussion

Data from this cross-sectional study showed that the COVID-19 related in-hospital death rate was higher among subjects with than without DM. Moreover, DM was independently associated with the risk of in-hospital case fatality and the composite outcome death or IMV. In the DM subgroup, both outcomes were predicted by older age, male sex, and pre-existing CKD. Finally, we observed a non-linear relationship between BG levels on admission and the probability of death and death or IMV in the overall inpatient population.

Diabetes is more frequent among subjects with COVID-19 needing hospital admission than those that do not, with prevalence ranging between 8% and 37% depending on the region [12]. Indeed, while the prevalence of DM in Spain has been estimated to be 13.8% of the general population, DM was present in 21.7% of the hospitalised subjects in our study. This figure is in line with the 18.9% prevalence reported in a retrospective cohort registry involving 109 hospitals in Spain [20]. It also concurs with the 16.7% recently published for the first COVID-19 wave by the working group for the surveillance and control of COVID-19 in Spain [21]. It is as well within the DM prevalence range reported by a meta-analysis of international studies (mean 13.4%, ranging between 7.2% and 21.3%) [22].

In the overall population, the in-hospital mortality rate was 14.5%, which is within the range of 7.2%-25.6% reported in available studies conducted in Spain [23-25]. This wide variation of case fatality between studies and centres has been observed worldwide, with rates varying widely between 4% and 60.5% and large differences even within the same country or region [7]. As for DM subjects, about a third (26.3%) of them died during the hospital stay in our study, which is high compared to the 20.4% reported by another Spanish study [20] and also higher than the one found

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by one French and two Chinese studies (20.4%, 10.6%, and 8.0%-14.5%, respectively) [26-28]. In contrast, our rate was lower than this outcome in a population-based study from the UK in 23,804 COVID-19 patients with DM, where in-hospital deaths occurred in 31.4% of T2DM individuals [29]. Differences between studies and centres could be attributed to different treatment guidelines, manners of identifying individuals with diabetes, and different proportions of DM patients with severe *vs.* non-severe disease. Indeed, COVID-19 patients with DM are more severely ill at initial presentation and, when in hospital, they have a 2-fold higher risk of severe infection than those without DM [15]. In turn, the death rate in DM patients with a severe illness can be up to 3-fold higher than this of patients with a non-severe course [12, 15, 22]. 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 [11, 27, 30]. In the same line, studies assessing the phenotypic characteristics of COVID-19 patients with pre-existing DM have found that those with severe infection were older, had more comorbidities (i.e., cerebrovascular disease, CVD, hypertension, and COPD), and increased values of inflammation and endothelial and coagulation dysfunction markers (e.g., D-dimer, procalcitonin, and thrombocytopenia) than those without DM [26-28,31,32]. Our study confirms these findings, as the proportion of severe SARS-CoV-2 cases (e.g., requiring IVM or ICU admission) in the DM population was higher. They were more frequently male and over 65 years, had more comorbid conditions, and higher levels of inflammatory and endothelial and coagulation dysfunction markers than non-DM patients on admission.

Different meta-analyses have identified CKD as a risk factor for severity and in-hospital death in SARS-CoV-2 patients [7, 25, 22, 33]. Moreover, a recent study conducted in Danish hospital-diagnosed COVID-19 patients reported that kidney insufficiency was independently associated with progressive risk of severe disease or death [34]. Although it is difficult to distinguish whether poor outcomes are linked to acute kidney injury (AKI) developed during the course of the disease

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or to pre-existing CKD [34], a study conducted in Spain showed that patients with either increased creatinine on admission, previous CKD, or developing AKI, had a higher risk of in-hospital death than those with normal creatinine on admission [35]. Of note, the authors found that older age and diabetes, but not other comorbidities, were associated with in-hospital death [35]. Finally, a study conducted in Mexico reported that patients with DM and CKD had a 2-fold higher rate of intubation, 56% higher ICU admission, and 21% excess probability of case-fatality once admitted than subjects with CKD alone [36]. These findings would be in line with those of our study, where patients with DM had significantly higher creatinine on admission, lower eGFR, and more frequently pre-existing CKD than non-DM subjects. Besides, CKD was the only comorbid condition increasing the odds (three-fold increase) of in-hospital death (and death or IMV) among the DM cohort after adjusting for age, sex, and confounding variables.

A recent dose-response meta-analysis reported that high admission fasting blood glucose (FBG) levels are significantly associated with COVID-19 severity, mortality, and poor outcome regardless of pre-existing DM [37]. Moreover, the results demonstrated a non-linear relationship between admission FBG level and infection severity [37]. These results confirm previous observations that FBG on admission and the odds of being admitted to the ICU follow a logarithmic association, with different magnitudes of risk depending on the baseline level [38]. Indeed, small FBG increases across the normal range were associated with a large increase in ICU admission risk, while equivalent increases in the high glucose range lead to a much lower increase in the risk. In our study, we used splines as a scientific and preferable alternative to the categorization of BG levels. We add to the literature that, besides the previously reported effect of hyperglycaemia on the risk of COVID-19 severity and ICU admission, BG has a non-linear relationship with case fatality and the risk of death or IVM. Of note, a recent report also identified glycaemic fluctuation as independently associated with poor prognosis and mortality in COVID-19 hospitalized patients [39]. In the same vein, a study on ICU patients showed that less time spent in range (70–150 mg/dL; 3.9-8.3 mmol/L)

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was associated with increased utilization of a ventilator, prolonged mechanical ventilation, and increased mortality [40]. Most importantly, a spline analysis of glucose levels in DM patients with continuous glucose monitoring showed a non-linear relationship between time spent above range and glycaemic variability with the increased likelihood of composite adverse COVID-19 outcomes (need for ICU admission, mechanical ventilation, or critical illness) [41]. Therefore, it is possible that the association of high BG on admission with death or IMV observed in our study was as well accompanied or reflecting glycaemic variability and less time spent in range.

4.1 Limitations of this study

The findings of this study must be interpreted with caution and a number of limitations should be borne in mind. Firstly, we had limited data for COVID19 infected persons. For instance, we did not have access to the patient's medical history prior to admission; so that the possibility exists that some important medical conditions were not included in the emergency room medical report and therefore not included in the analysis. Secondly, we had very few registers for some important variables for diabetes, such as Hb1Ac (only data from 36 patients) and no data on weight or BMI (only the presence of obesity). Thirdly, the selection of subjects with DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and $HbA1_c$ and blood glucose levels), which could have introduced selection or referral bias, potentially leading to an inaccurate estimation of DM prevalence. Fourthly, and inherent to data coming from hospital medical records, missing values could have reduced the statistical power of the study or produced biased estimates. Fifthly, we used random BG on admission for the spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM. This also prevented the analysis of time in range or BG variability, both of them linked to increased severity, case fatality, and poor COVID-19 outcomes [39-41]. Lastly, the study period coincides with the height of the pandemic first wave in Spain, when there was shortage of ventilators and intensive care beds. By then, age was the deciding factor on whether or not someone

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received potentially life-saving ICU care. This might be reflected in our results, where in-hospital death was more frequent among those over 65 years, but ICU admission was more frequent among those ≤65 years.

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5. Conclusions

The results in our study confirm the high burden associated with DM in patients hospitalised because of SARS-CoV-2 infection. Comorbid DM poses a challenge to the health professionals and system because it is associated with severe disease, higher ICU admission rates, IMV, and ultimately death, particularly among the elderly. The non-linear relationship of hyperglycaemia at admission with increased odds of death and IVM suggests that optimizing glycaemic control during the hospital stay could help to reduce in-hospital death and the composite death/IVM. Besides, out-of-hospital care should be a priority to reduce or prevent uncontrolled glycaemia among those with DM as it could potentially help reduce poor outcomes when hospitalisation is needed.

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Table 1. *Baseline characteristics of the studied cohorts at hospital admission*

Characteristic	DM N=448	Non _DM N=1621	p-value
Age, mean (SD), years	71.7 (11.9)	66.6 (16.3)	<0.001
Age, median (P25, P75), years	72.0 (64.0; 80.0)	67.0 (55.0; 79.0)	<0.001
Gender (male), n (%)	304 (67.9)	950 (58.6)	<0.001
Glucose, mean, (SD) mg/dL mmol/L	 168 (74.4) 9.3 (4.1)	 112 (24.8) 6.2 (1.4)	<0.001
Comorbidities, n (%)			
Hypertension	224 (50.0)	427 (26.3)	<0.001
Hyperlipidaemia	154 (34.4)	255 (15.7)	<0.001
Obesity	45 (10.0)	72 (4.44)	<0.001
Cardiovascular diseases	28 (6.25)	49 (3.02)	0.002
Heart failure	18 (4.02)	33 (2.04)	0.026
Cerebrovascular diseases	10 (2.23)	17 (1.05)	0.086
Ischemic heart disease	18 (4.02)	29 (1.79)	0.009
Chronic kidney disease	30 (6.70)	46 (2.84)	<0.001
COPD	34 (7.59)	78 (4.81)	0.029
Asthma	0 (0.00)	2 (0.12)	1.000
Mental disorders	35 (7.81)	79 (4.87)	0.022
Cancer	36 (8.04)	81 (5.00)	0.019

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; P25, P75, 25th and 75th percentile, respectively; SD, standard deviation

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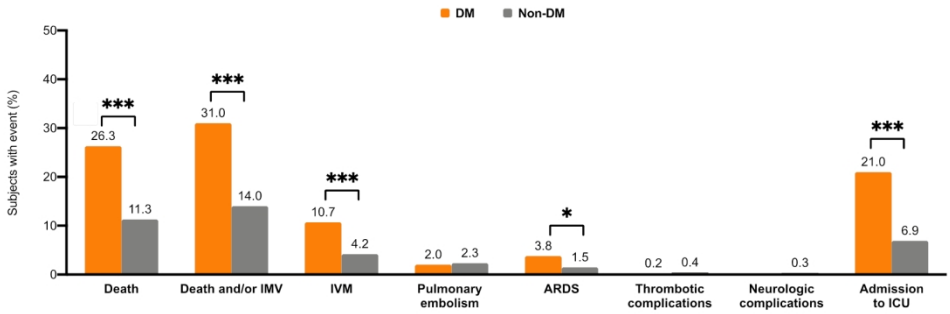

Figure 1. Proportion of events (%) during hospitalization according to the presence of diabetes.

ARDS, acute respitarory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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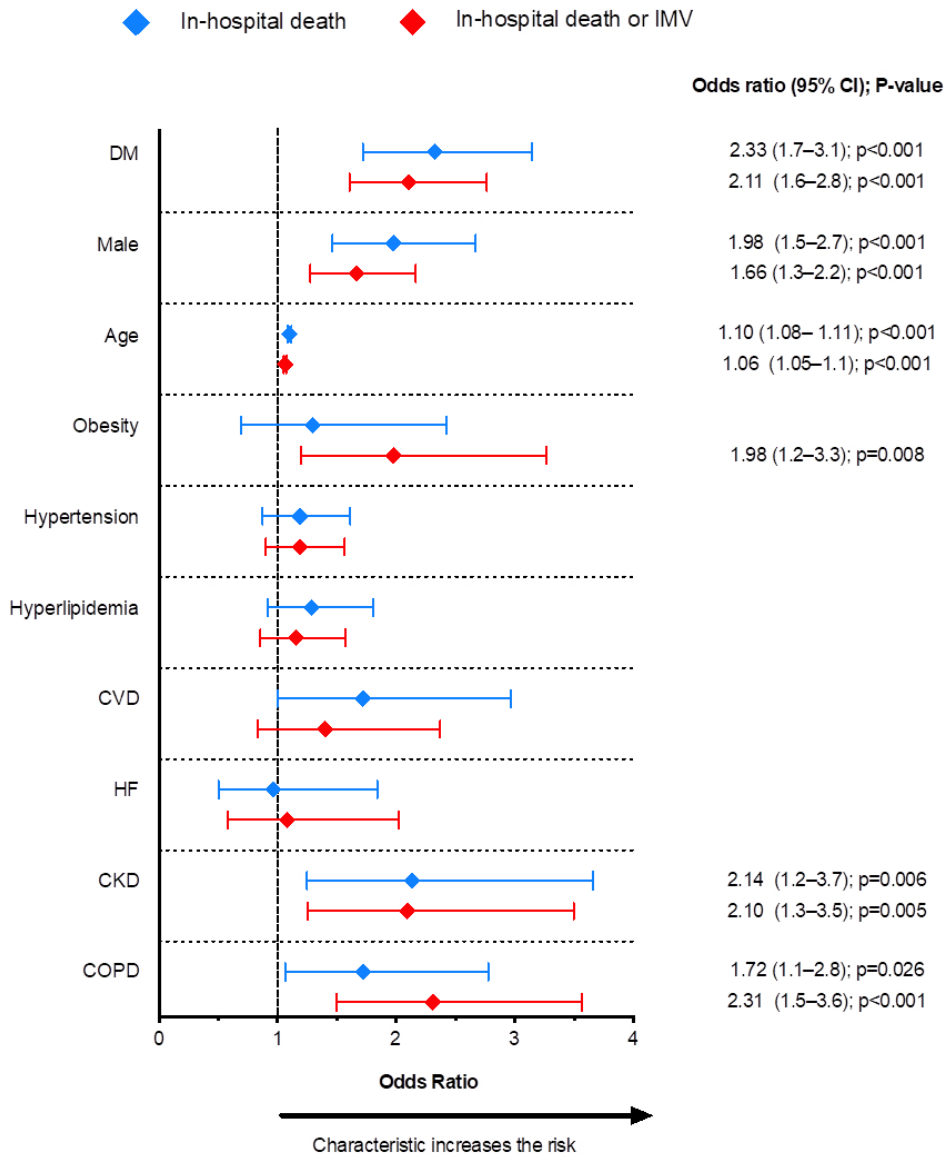

Figure 2. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death or invasive mechanical ventilation.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

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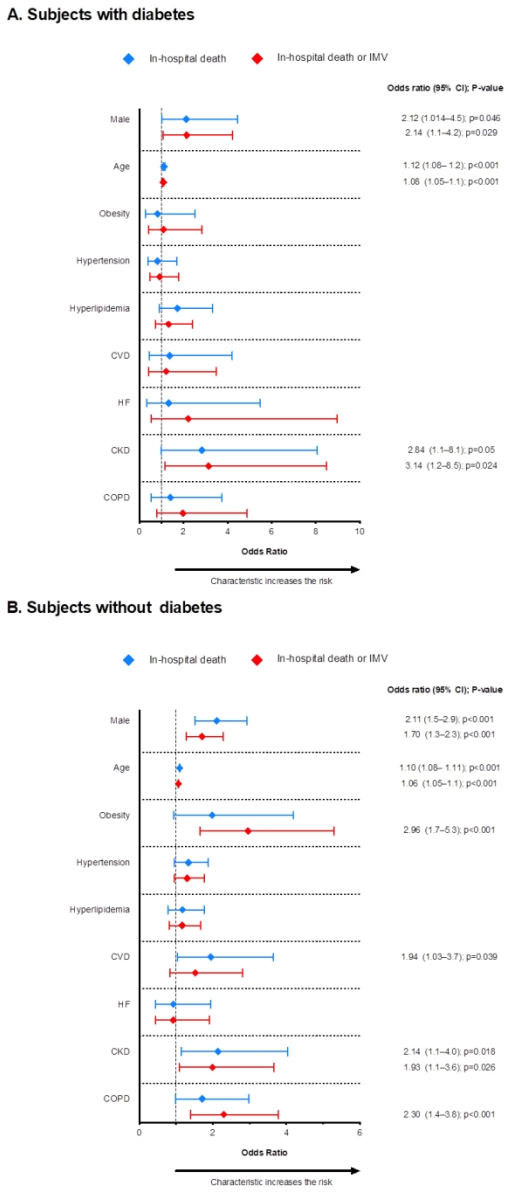

Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes (A) and without diabetes (B).
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

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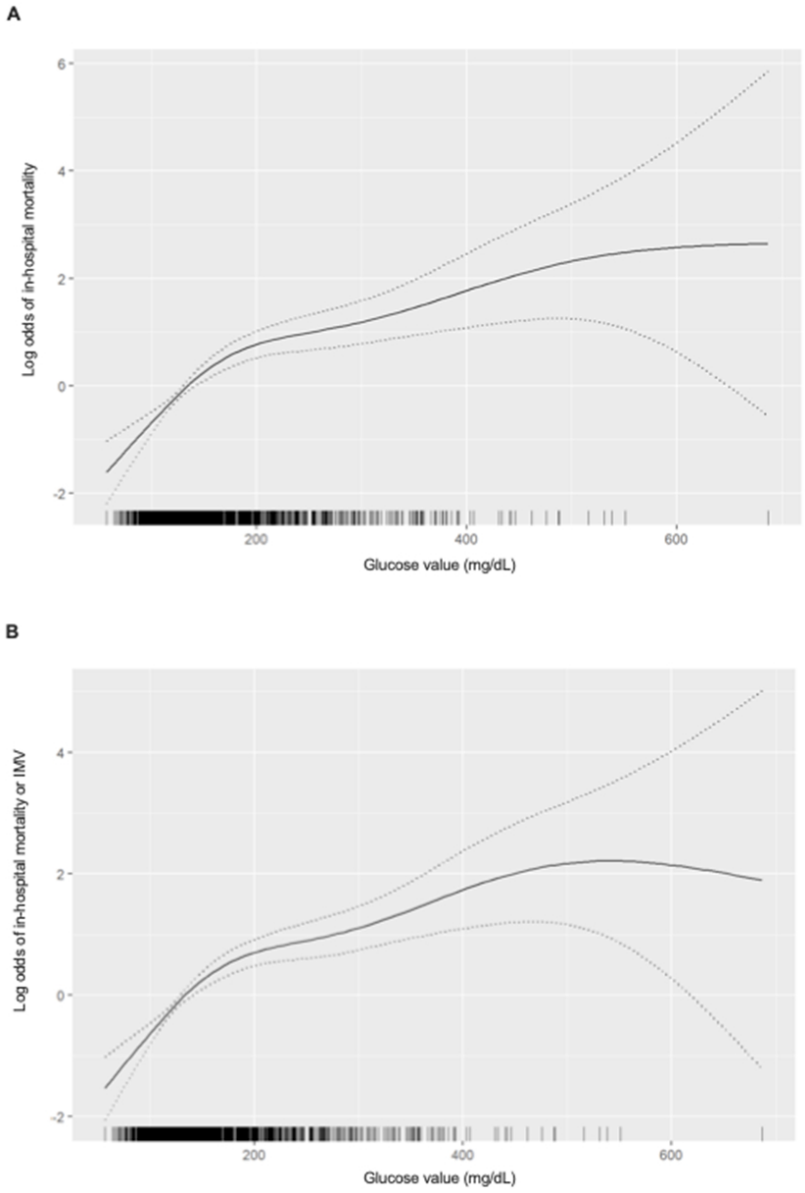

Figure 4. Spline plot demonstrating a marked non-linearity in the relationship between plasma random glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive mechanical ventilation (IMV) rate (B). Tick marks above the horizontal axis indicate the values at which the observations were made. The dotted lines represent the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD.

IMV, intensive mechanical ventilation

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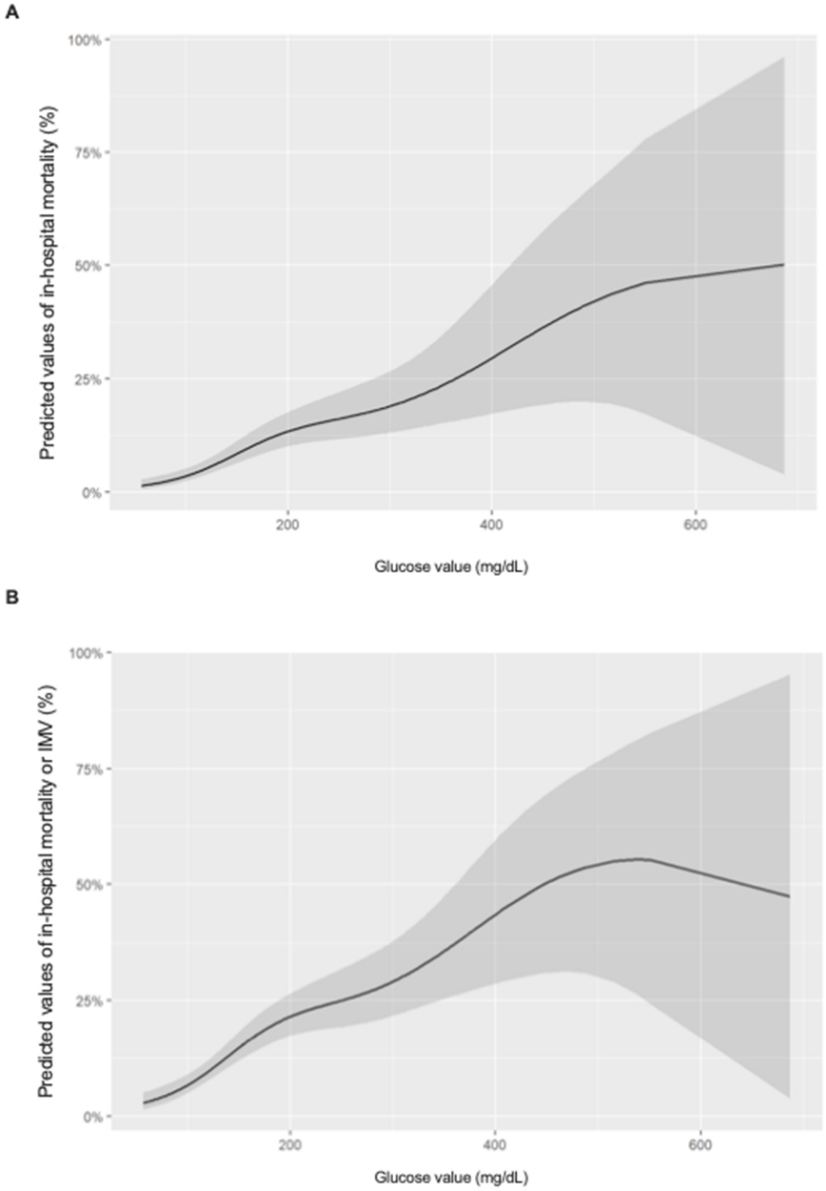

Figure 5. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized smoothing splines. The shaded area represents the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD

IMV, intensive mechanical ventilation

231x333mm (96 x 96 DPI)

ONLINE-ONLY SUPPLEMENTARY MATERIALS

These supplemental materials have been provided by the authors to give the readers additional information about the study.

Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19

Emilio Ortega [1,2,3], Rosa Corcoy [4,5,6], Mònica Gratacòs[1], Xavier Cos-Claramunt [1,7], Manel Mata-Cases [1,8,10], Ramon Puig- Treserra[1], Jordi Real [1], Bogdan Vlacho [1], Esmeralda Castelblanco [1,8,], Pere Domingo [9], Kamlesh Khunti [11], Josep Franch-Nadal [1,8,12*] and Dídac Mauricio [1,4,8,13*]

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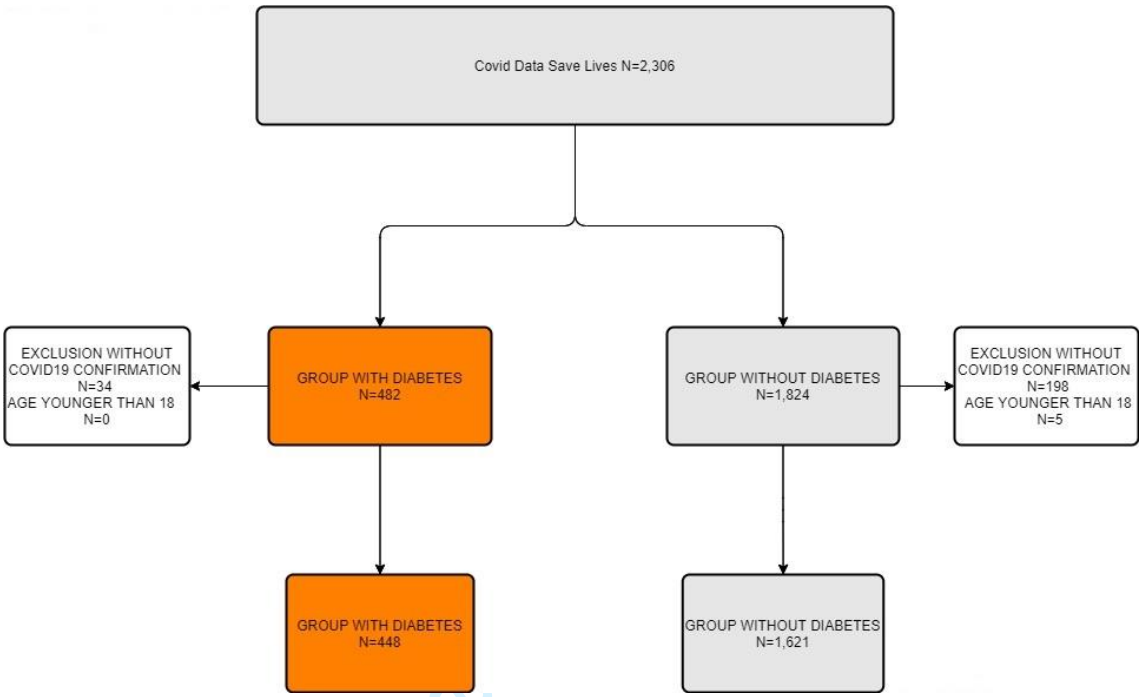
Supplementary Figure 1. Flowchart diagram



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Supplementary Table 1. Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus

	With diabetes N=448	**Without diabetes N=1621**	p-value
Vital signs			
Systolic blood pressure, mean, (SD), mmHg	128 (19.7)	123 (19.3)	0.037
Diastolic blood pressure, mean, (SD), mmHg	72.0 (12.1)	71.1 (12.5)	0.501
Heart rate, mean, (SD), bpm	80.2 (14.7)	79.4 (14.9)	0.641
Temperature, mean, (SD), °C	36.5 (0.823)	36.5 (0.805)	0.086
Basal laboratory measurements			
Glomerular filtration (CKD-EPI), mean, (SD), mL/min/1.73 m²	73.5 (26.5)	81.2 (23.9)	<0.001
Creatinine, mean, (SD), mg/dL	1.09 (0.716)	0.943 (0.510)	<0.001
Procalcitonin, mean, (SD), ng/mL	0.661 (1.30)	0.387 (1.30)	<0.001
D-dimer, mean, (SD), ng/mL	3990 (10800)	2340 (6720)	<0.001
Alkaline phosphatase, mean, (SD), U/L	78.3 (39.1)	78.6 (62.3)	0.984
Lactate dehydrogenase, mean, (SD), U/L	644 (399)	575 (311)	<0.001
C-reactive protein, mean, (SD), mg/L	97.1 (107)	75.9 (82.5)	<0.001
Gamma-glutamyl transferase, mean, (SD), U/L	93.8 (135)	88.4 (123)	0.804
Aspartate aminotransferase, mean, (SD), U/L	49.6 (165)	42.7 (57.8)	0.022
Alanine aminotransferase, mean, (SD), U/L	51.7 (136)	45.1 (60.6)	0.354
Haemoglobin, mean, (SD), g/dL	13.1 (2.09)	13.6 (1.84)	0.433
Leucocytes, mean, (SD), x10e3/µL	8.91 (6.52)	7.47 (4.17)	<0.001
Platelets, mean, (SD), x10e3/µL	247 (112)	250 (116)	0.705
Prothrombin time, mean, (SD), s	15.6 (15.6)	14.8 (10.5)	0.076
Monocytes, mean, (SD), %	7.21 (5.29)	8.19 (3.91)	<0.001
Lymphocytes, mean, (SD), %	15.6 (10.0)	19.0 (10.9)	<0.001
Neutrophils, mean, (SD), %	76.1 (13.5)	71.8 (13.5)	<0.001
Phosphorus, mean, (SD), mg/dL	3.39 (0.971)	3.15 (0.731)	0.026
Sodium, mean, (SD), mg/dL	138 (6.41)	138 (4.35)	0.537
Calcium, mean, (SD), mg/dL	8.31 (0.648)	8.39 (0.574)	0.102

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PCO2 – pCO2., mean, (SD), mmHg	37.8 (9.95)	35.8 (7.42)	0.007
PO2 – pO2, mean, (SD), mmHg	73.4 (35.4)	67.5 (30.9)	0.216
SO2C – Oxigen saturation, mean, (SD), %	90.3 (11.4)	89.1 (13.6)	0.694

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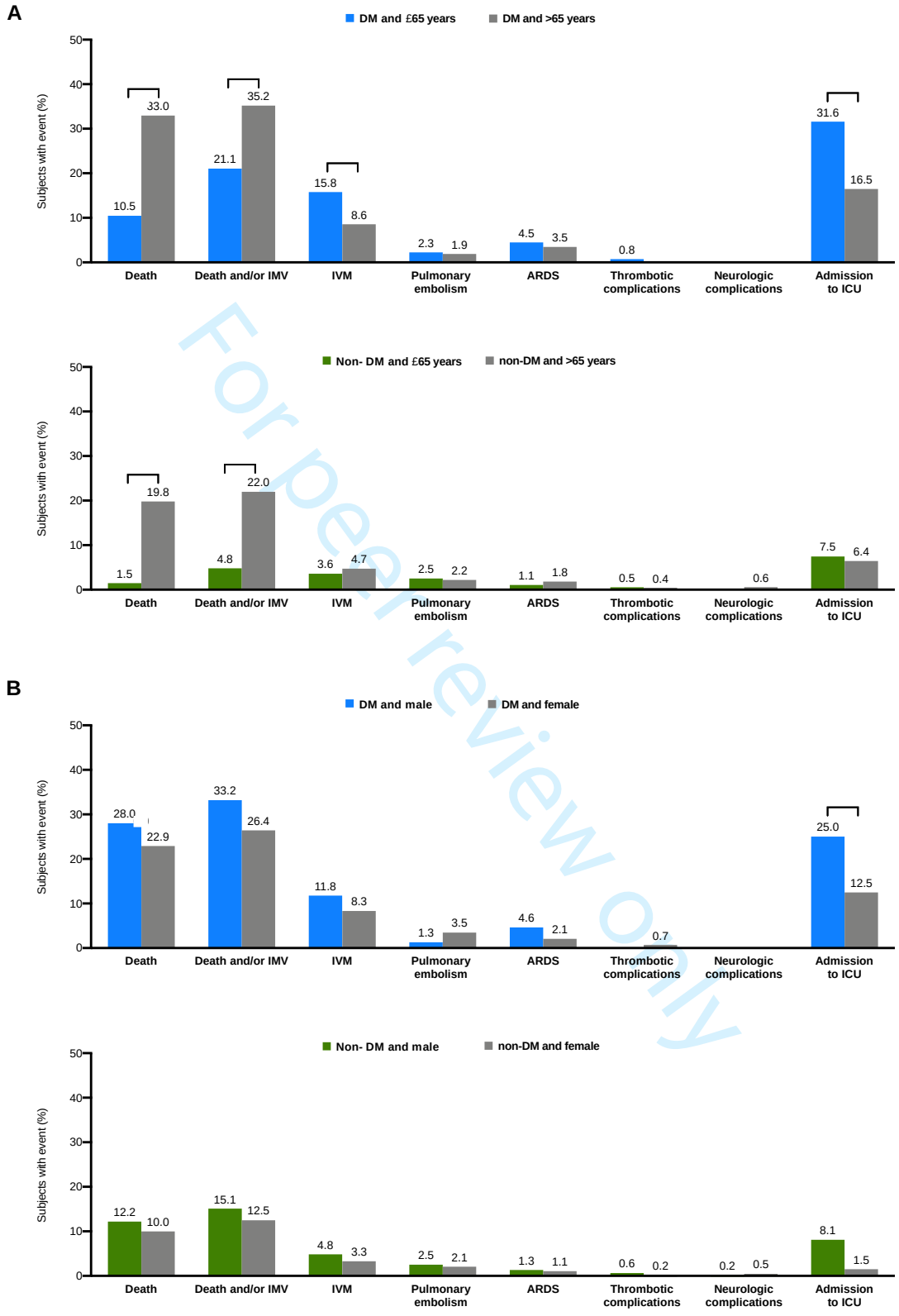
Supplementary Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).



ARDS, acute respitarory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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Supplementary Table 2. Clinical characteristics at baseline as predictors of death vs death or invasive mechanical ventilation according to the model with all potential independent variables included

	Death			Death or invasive mechanical ventilation		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Diabetes (yes)	2.325 ***	1.719–3.144	<0.001	2.107 ***	1.608–2.761	<0.001
Sex (male)	1.977 ***	1.463–2.670	<0.001	1.663 ***	1.276–2.167	<0.001
Age (years)	1.102 ***	1.087–1.117	<0.001	1.063 ***	1.052–1.075	<0.001
Obesity (yes)	1.297	0.694–2.424	0.414	1.978 **	1.198–3.267	0.008
Hypertension (yes)	1.188	0.874–1.613	0.271	1.188	0.902–1.565	0.221
Hyperlipidaemia (yes)	1.289	0.919–1.808	0.141	1.158	0.853–1.572	0.346
Cardiovascular diseases (yes)	1.721	0.999–2.966	0.051	1.403	0.830–2.370	0.206
Heart failure (yes)	0.964	0.504–1.842	0.911	1.082	0.578–2.023	0.806
Chronic renal insufficiency (yes)	2.135 **	1.246–3.659	0.006	2.096 **	1.255–3.498	0.005
COPD (yes)	1.721 *	1.066–2.779	0.026	2.310 ***	1.498– .564	<0.001
Observations	2069			2069		
R2 Tjur	0.208			0.157		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 3. Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.

	Death		
Predictors	Odds Ratios	95% CI	p-value
Diabetes * Obesity	0.720	0.214–2.425	0.596
Diabetes * Hyperlipidaemia	0.766	0.407–1.442	0.408
Diabetes * Heart failure	1.406	0.373–5.298	0.614
Diabetes * Chronic kidney disease	0.805	0.273–2.371	0.693
Diabetes * COPD	0.631	0.235–1.696	0.361

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Supplementary Table 4. Clinical characteristics at baseline associated with in-hospital death stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	2.107 ***	1.516–2.929	<0.001	2.125 *	1.014–4.451	0.046
Age	1.096 ***	1.081–1.112	<0.001	1.124 ***	1.081–1.170	<0.001
Obesity	1.984	0.938–4.198	0.073	0.826	0.272–2.511	0.736
Hypertension	1.333	0.947–1.876	0.099	0.823	0.400–1.697	0.598
Hyperlipidaemia	1.173	0.780–1.765	0.443	1.729	0.899–3.326	0.101
Cardiovascular diseases	1.943 *	1.033–3.654	0.039	1.368	0.445–4.208	0.584
Heart failure	0.926	0.442–1.944	0.840	1.330	0.323–5.484	0.693
Chronic kidney disease	2.143 *	1.137–4.038	0.018	2.839 *	1.000–8.060	0.050
COPD	1.712	0.984–2.979	0.057	1.404	0.529–3.729	0.495
Observations	1795			274		
R2 Tjur	0.178			0.240		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 5. Clinical characteristics at baseline associated to in-hospital death or mechanical ventilation stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	1.710 ***	1.282–2.280	<0.001	2.138 *	1.081–4.226	0.029
Age	1.061 ***	1.050–1.073	<0.001	1.082 ***	1.047–1.118	<0.001
Obesity	2.958 ***	1.651–5.298	<0.001	1.090	0.420–2.827	0.860
Hypertension	1.297	0.955–1.762	0.096	0.920	0.473–1.789	0.806
Hyperlipidaemia	1.165	0.811–1.675	0.408	1.326	0.728–2.415	0.356
Cardiovascular diseases	1.525	0.827–2.814	0.177	1.217	0.426–3.477	0.714
Heart failure	0.923	0.447–1.906	0.829	2.219	0.549–8.971	0.264
Chronic kidney disease	1.993 *	1.084–3.662	0.026	3.140 *	1.163–8.474	0.024
COPD	2.298 **	1.396–3.781	0.001	1.976	0.800–4.885	0.140
Observations	1795			274		
R2 Tjur	0.129			0.190		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 6. Multivariate model of the association between predictors and the odds of death and death or invasive mechanical ventilation based on the nonlinear glucose curve.

	Death			Death or Invasive mechanical ventilation		
Predictors	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Sex (male)	1.911 ***	1.375–2.655	<0.001	1.540 **	1.159–2.047	0.003
Age	1.108 ***	1.090–1.125	<0.001	1.062 ***	1.049–1.074	<0.001
Obesity	1.079	0.527–2.206	0.836	1.814 *	1.057–3.112	0.031
Hypertension	1.109	0.800–1.537	0.534	1.134	0.849–1.515	0.394
Hyperlipidaemia	1.330	0.928–1.906	0.120	1.152	0.837–1.585	0.386
Cardiovascular diseases	1.686	0.958–2.967	0.070	1.356	0.792–2.325	0.267
Heart failure	0.768	0.388–1.520	0.448	0.911	0.472–1.757	0.781
Chronic kidney disease	2.251 **	1.268–3.996	0.006	2.151 **	1.250–3.701	0.006
COPD	1.666 *	1.006–2.760	0.047	2.253 ***	1.436–3.536	<0.001
s(Glucose)	29.254 ***		<0.001	33.307 ***		<0.001
Observations			1877			1877
R2			0.241			0.188

p<0.05 ** p<0.01 *** p<0.001

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Supplementary figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Figure 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 2, Supplementary table2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12,13 Supplementary table 3,4,5
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

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Abstract:

Aim: This study's objective was to assess the risk of severe in-hospital complications of patients admitted for coronavirus disease (COVID-19) and diabetes mellitus (DM).

Design: This was a cross-sectional study

Settings: We used pseudonymised medical record data provided by six general hospitals from the HM Hospitales group in Spain.

Outcome measures: Multiple logistic regression analyses were used to identify variables associated with mortality and the composite of mortality or invasive mechanical ventilation (IMV) in the overall population, and stratified for the presence or absence of DM. Spline analysis was conducted on the entire population to investigate the relationship between glucose levels at admission and outcomes.

Results: Overall, 1,621 individuals without DM and 448 with DM were identified in the database. DM patients were on average 5.1 years older than those without. The overall in-hospital mortality was 18.6% (N=301), and was higher among patients with DM than without (26.3% *vs.* 11.3%; p<0.001). DM was independently associated with death, and death or IMV (OR=2.33, 95% CI: 1.7–3.1 and OR=2.11, 95% CI: 1.6– 2.8, respectively; p<0.001). In DM subjects, the only variables independently associated with both outcomes were age >65 years, male sex, and pre-existing chronic kidney disease (CKD). We observed a non-linear relationship between blood glucose levels at admission and risk of in-hospital mortality and death or IMV. The highest probability for each outcome (around 50%) was at random glucose of around 550 mg/dL (30.6 mmol/L), the risks flattened above this value.

Conclusion: The results confirm the high burden associated with DM in patients hospitalized with COVID-19 infection, particularly among males, the elderly, and those with impaired kidney

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function. Moreover, hyperglycaemia on admission was strongly associated with poor outcomes, suggesting that personalised optimisation could help to improve outcome during the hospital stay.

Keywords: COVID-19, Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation

Strengths and limitations of this study

- A major strength of our study is the thorough methodological approach to analyse the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia.
- We were limited by not having access to the patients' medical history prior to admission, and the low number of registers for some important DM variables (such as Hb1Ac), and the lack of data on weight or BMI (only the presence of obesity).
- The selection of DM subjects was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose levels at admission.
- We used random blood glucose on admission for spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.

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1. Introduction

On January 30, 2020, the World Health Organization (WHO) declared the outbreak of the novel SARS-CoV-2 coronavirus pandemic, a public health emergency of international importance. A few days later, the respiratory disease caused by SARS-CoV-2 was officially named COVID-19 (Corona Virus Infectious Disease 2019) [1, 2]. The first person diagnosed as positive in Spain was confirmed on January 31, 2020, on the island of La Gomera [3]. The median age of hospitalized patients infected with SARS-CoV-2 is 46.2 years, men comprise about 60% of patients, and the average incubation period is 5.7 days [4]. As of February 8, 2021, approximately 3 million people have been infected with SARS-CoV-2 in Spain since the start of the COVID-19 pandemic, and 62,295 persons have died.

Several meta-analyses have reported that the most severe and fatal cases of COVID-19 occur among the elderly and in patients with underlying comorbidities [5-7]. Indeed, those with two or more concomitant diseases have a significantly higher risk of admission to an intensive care unit (ICU), invasive ventilation, or death compared with those with a single concomitant disease, or without comorbidities [8]. The most prevalent comorbidities associated with increased COVID-19-related morbidity and mortality are the presence of diabetes mellitus (DM), cardiovascular diseases (CVDs), chronic lung disease, chronic kidney disease (CKD), hypertension, cancer, and obesity [5-7]. 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].

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

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with the cellular membrane [10]. Although it was initially assumed that ACE inhibitors and angiotensin receptor blockers to treat hypertension or cardiovascular conditions 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.

Previous studies have reported that people with DM are prone to new infections and recurrence, particularly influenza and pneumonia, due to impaired defences and disease complications [13-16]. Although the estimated prevalence of DM in COVID-19 infected patients varies greatly by geographical region, it is considered similar to the DM prevalence in the general population, thus not representing a risk factor for infection [17]. However, the prevalence of diabetes among COVID-19 hospitalized subjects is higher than the overall diabetes prevalence [17, 18]. A study conducted in England found that a third of in-hospital deaths occurred in people with type 2 DM and that these patients had greater odds of COVID-19-related in-hospital death than those without DM [19]. This observation has been confirmed in a meta-analysis showing that DM is associated with a 2-fold higher risk of dying from COVID-19 [20], and a second study reporting that patients with pre-existing DM have a 3-fold greater risk of in-hospital mortality [21].

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].

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In Spain, DM is a highly prevalent disease in people over 18 years of age (13.8% of the population) [27]. Given the high prevalence of DM and the additional challenging scenario that COVID-19 poses to health care professionals in this particular population, it is crucial to accumulate and share information and data from different countries and regions [28]. Following this notion, the main objective of this study was to assess the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia at admission in Spain.

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2. Methods

2.1 Study design and settings

This was a cross-sectional study in hospitalized individuals infected with SARS-CoV-2, stratified by presence or absence of DM. Data were obtained from pseudonymized electronic health records provided by six general hospitals from the HM Hospitales group (Spain). 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 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. Detailed information related to the database is presented in the Supplementary material (**Database description**).

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. The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol, Barcelona (approval number: 20/089-PCV).

2.2 Inclusion and Exclusion Criteria

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

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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.

2.3 Study Variables

The following baseline variables were collected: age and sex; SARS-CoV-2 diagnosis (positive RT-PCR); comorbidities (i.e., hypertension, hyperlipidaemia, obesity [BMI ≥30 kg/m^2], CVD, heart failure, cerebrovascular diseases, ischemic heart disease, CKD, chronic obstructive pulmonary disease [COPD], asthma, mental disorders, and cancer); blood laboratory parameters (i.e., HbA1c, BG, electrolytes, renal function, liver function, haematology and coagulation, inflammation markers, and gas tests); clinical parameters (i.e., systolic and diastolic blood pressure, heart rate, and temperature), and concomitant medications (i.e., baseline insulins, systemic corticosteroids, antimicrobials, anticoagulants and antiplatelet agents, and antihypertensive and lipid-lowering drugs).

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.

2.4 Statistical Methods

The demographic and clinical characteristics of the two groups of hospitalized patients (i.e., with or without DM) were compared and summarized at the quantitative (minimum, maximum, median, first and third quartile, mean, and standard deviation [±SD]) or categorical level (frequency, number and %).

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The association between the study outcomes (i.e., mortality and mortality or mechanical ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and associated risk factors. 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 the respective 95% confidence intervals (CI). We evaluated goodness of fit of the logistic regression models with H&L test (Hosmer–Lemeshow test). To analyse the nonlinear relationship of random blood glucose levels on admission with the two study outcomes, we used an adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves with two degrees of freedom (knots) using the mgcv package in R, version 1.8-31[29] with adjustment for potential confounders. We analysed the entire database available and no statistical power was calculated. Data management and statistical analyses were performed using the R statistical software version 3.6.1 (https://www.r-project.org/).

2.5 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

3.1. Baseline Characteristics

Of the 2,306 subjects admitted to hospital within the period of study, 2,069 were over 18 years of age and had a positive diagnostic test for SARS-CoV-2 (**Figure 1**). Among them, 448 (21.7%) were identified as having DM and 1,621(78.3%) without DM (non-DM group). The characteristics of the two populations at hospital admission are shown in **Table 1**. Subjects with DM were on average 5.1 years older than non-DM subjects, and more frequently male (67.9% *vs.* 58.6%). Moreover,

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individuals in the DM group had a poor comorbidity profile, with a higher frequency of all assessed prior conditions except for cerebrovascular diseases and asthma.

Regarding laboratory parameters on admission (**Supplementary Table 1)**, the DM group had slightly lower estimated glomerular filtration rates (eGFR) (73.5±26.5 mL/min/1.73 m^2 *vs.* 81.2±23.9 mL/min/1.73 m^2; p<0.001), and higher levels of serum creatinine (1.09±0.72 mg/dL *vs.* 0.94±0.51 mg/dL; p<0.001) than the non-DM group. Regarding markers of inflammation and infection, we observed higher levels of C-reactive protein and procalcitonin in the DM group (97.1±107 mg/L *vs.* 75.9± 82.5 mg/L and 0.66±1.30 mg/L *vs.* 0.39±1.30 mg/L, respectively; p<0.001). We also observed higher levels of D-dimer, a marker of endothelial and coagulation dysfunction in the DM group (3990 ±10800 ng/mL *vs* .2340 ±6720 ng/mL, respectively). 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.

3.2 Events and complications during in-hospital stay

A total of 301 (14.5%) subjects positive for SARS-CoV-2 died in-hospital, 118 (26.3%) out of 448 in the DM group and 183 (11.3%) out of 1621 in the non-DM group (p<0.001; **Figure 2**). All studied events, except pulmonary embolism and thrombotic or neurologic complications, were significantly more frequent among patients with DM than without (**Figure 2**). The most frequent outcome was the composite of death or IMV (31% in the DM group *vs.* 14% in the non-DM group; **Figure 2**) 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%).

The frequency of events by group and age showed that, in both subjects with and without DM, death and the composite of death or IMV were significantly more frequent among those >65 years (**Supplementary Figure 1**). In contrast, the proportion of subjects requiring IMV and ICU admission

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was significantly higher among those ≤65 years and with DM, while age was not significant in those without DM. 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**). 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.**

3.3. Baseline demographic and clinical characteristics associated with in-hospital death and death or IMV

For the overall hospitalized population, the demographic characteristics significantly associated with mortality were male sex and older age (OR=1.98, 95% CI=1.2–3.3 and OR=1.10, 95% CI=1.08–1.11, respectively) (**Figure 2; Supplementary Table 2**). The comorbidities independently associated with increased odds of death were DM (OR=2.33, 95% CI=1.7–3.1), CKD (OR=2.14, 95% CI=1.2–3.7), and COPD (OR=1.72, 95% CI=1.1–2.8).

When considering the composite outcome of death or IMV, the same variables associated with death (i.e., age, sex, diabetes, CKD, and COPD) were identified as increasing the risk. In addition, obesity emerged as an independently associated variable (OR=1.98, 95% CI=1.5–2.7) (**Figure 3**, **Supplementary Table 3).**

The multiple logistic regression models were repeated to rule out the potential interaction of DM with different clinical conditions (i.e., obesity, hyperlipidaemia, obesity and hyperlipidaemia, heart failure, CKD, and COPD) for the in-hospital death outcome. The results showed that none of these conditions affected the relationship between the risk of death and DM (**Supplementary Table 4**).

3.4. Factors associated with hospital death and death or IMV by comorbid diabetes

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A sub-analysis was performed separately for subjects with or without DM. In the DM group, the only variables independently associated with the risk of both mortality and death or IMV were male sex, older age, and CKD (**Figure 4A** and **Supplementary Table 5** and **6**). In contrast, in subjects without DM, besides the aforementioned variables, the odds of death were also increased among subjects with CVD (OR=1.94, 95% CI=1.03– 3.7), and the odds of death or IMV among those with obesity or COPD (OR=2.96, 95% CI=1.7–5.3 and OR=2.30, 95% CI= 1.4 – 3.8, respectively) (**Figure 4B** and **Supplementary Table 5** and **6)**.

3.5. Factors associated with hospital death and death or IMV by glucose levels at admission

We used non-parametric logistic regression models to assess whether there was a relationship between random BG on admission and the risk of mortality (and death or IMV). We observed a marked non-linearity in the effect of BG on admission in the risk of both outcomes (**Figure 5A and 5B** and **Supplementary Table 7**). While the risk was increased among subjects with high random BG levels on admission, the magnitudes of the associated mortality differed depending on the baseline values, with a large increase in the log-odds of death or IMV with values up to 200 mg/dL (11.1 mmol/L), and smaller increases above this level. The logistic regression models (**Figure 6A and 6B**) showed that the highest probability of death (near 50%) was at around 550 mg/dL (30.6 mmol/L) and, above this value, the mortality risk flattened. Finally, the multivariate model showed that, beside glucose at admission, male sex, older age, CKD, and COPD were associated with in-hospital death (**Supplementary Table 7**). These variables were linked to death or IMV too, but obesity was an additional risk factor (**Supplementary Table 7**).

4. Discussion

Data from this cross-sectional study showed that the COVID-19 related in-hospital death rate was higher among subjects with DM than without. Moreover, DM was independently associated with the risk of in-hospital case fatality and the composite outcome, death or IMV. In the DM group,

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both outcomes were associated with older age, male sex, and pre-existing CKD. Finally, we observed a non-linear relationship between BG levels on admission and the probability of death and death or IMV in the overall inpatient population.

In our study, the proportion of severe COVID-19 cases (e.g., requiring IMV or ICU admission) in the DM population was higher than in the non-DM cohort. Moreover, DM patients were more frequently male and over 65 years, had more comorbid conditions, and higher levels of inflammatory, endothelial, and coagulation dysfunction markers on admission. Different meta-analyses have reported that older age and male sex are characteristics associated with severe COVID-19 infection and high fatality rates [17, 30, 31]. Along the same line, studies assessing the phenotypic characteristics of COVID-19 patients with pre-existing DM have found that those with severe infection were older, had more comorbidities (i.e., cerebrovascular disease, CVD, hypertension, and COPD), and increased values of inflammation, endothelial and coagulation dysfunction markers (e.g., D-dimer, procalcitonin, and thrombocytopenia), than those without DM [30- 35].

In our study, patients with DM had significantly higher creatinine on admission, lower eGFR, and more frequently pre-existing CKD than non-DM subjects. Besides, CKD was the only comorbid condition increasing the odds (three-fold increase) of in-hospital death (and death or IMV) among the DM cohort after adjusting for age, sex, and confounding variables. Different meta-analyses have identified CKD as a risk factor for severity and in-hospital death in SARS-CoV-2 infected patients [7, 36 -38]. 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 [39]. Although it is difficult to distinguish whether poor outcomes are linked to acute kidney injury (AKI) developed during the course of the disease, or to pre-existing CKD [39], a study conducted in Spain showed that patients with increased creatinine on admission, previous CKD, or

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developing AKI, had a higher risk of in-hospital death than those with normal creatinine on admission [40]. Of note, the authors found that older age and diabetes, but not other comorbidities, were associated with in-hospital death [40]. Finally, a study conducted in Mexico reported that, patients with DM and CKD had a 2-fold higher rate of intubation, 56% higher ICU admission, and 21% excess probability of case-fatality once admitted, than subjects with CKD alone [41].

In our study, we used splines as a scientific and preferable alternative to the categorization of BG levels [42]. We used this approach because a recent dose-response meta-analysis demonstrated a non-linear relationship between admission fasting blood glucose (FBG) level and COVID-19 severity, with high levels being significantly associated with increased mortality and poor outcome, regardless of pre-existing DM [43]. These results confirmed previous observations that FBG on admission, and the odds of being admitted to the ICU, followed a logarithmic association, with different magnitudes of risk depending on the baseline level [42]. We add to the literature that, besides the previously reported effect of hyperglycaemia on the risk of COVID-19 severity, ICU admission, and mortality [24,25], BG has a non-linear relationship with case fatality and the risk of death or IMV. It is possible that this relationship was also accompanied by, or reflected glycaemic variability and less time spent in range. Indeed, glycaemic fluctuation has been reported to be independently associated with poor prognosis and mortality in COVID-19 hospitalized patients [44]. In the same vein, a study on ICU patients showed that the less time spent in range was associated with increased utilization of a ventilator, prolonged mechanical ventilation, and increased mortality [45]. Most importantly, a spline analysis of glucose levels in DM patients with continuous glucose monitoring showed a non-linear relationship between time spent above range and glycaemic variability with the increased likelihood of composite adverse COVID-19 outcomes (need for ICU admission, mechanical ventilation, or critical illness) [46].

4.1 Limitations of this study

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The findings of this study must be interpreted with caution and a number of limitations should be borne in mind. Firstly, we had limited data for SARS-CoV-2 infected persons. For instance, we did not have access to the patient's medical history prior to admission; so the possibility exists that some important medical conditions were not included in the emergency room medical report and, therefore, not included in the analysis. Moreover, data on socio-demographic characteristics (ethnicity, race, economic or educational status) and toxic habits (smoking, alcohol or drug use) were not available. 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 for 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. Thirdly, the selection of subjects with DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose levels), which could have introduced selection or referral bias, potentially leading to an inaccurate estimation of DM prevalence. Fourthly, and inherent to data coming from hospital medical records, missing values could have reduced the statistical power of the study, or produced biased estimates. Fifthly, we used random BG on admission for the spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM. This also prevented the analysis of time in range or BG variability, both being linked to increased severity, case fatality, and poor COVID-19 outcomes [42-46]. Lastly, the study period coincides with the height of the first pandemic wave in Spain, when there was a shortage of ventilators and intensive care beds. At this point, age was the deciding factor for whether or not someone received potentially life-saving ICU care. This might be reflected in our results, where in-hospital death was more frequent among those over 65 years, but ICU admission was more frequent among those ≤65 years.

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5. Conclusions

The results of our study confirm the high burden associated with DM in patients hospitalized due to SARS-CoV-2 infection. Comorbid DM poses a challenge to health professionals and the system because it is associated with severe disease, higher ICU admission rates, IMV, and ultimately death, particularly among the elderly. The non-linear relationship of hyperglycaemia at admission with increased odds of death and IMV suggests that, optimizing glycaemic control during the hospital stay could help to reduce in-hospital death and the composite death/IMV. Besides, out-of-hospital care should be a priority to reduce or prevent uncontrolled glycaemia among those with DM, as it could potentially help reduce poor outcomes when hospitalization is required.

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Table 1. *Baseline characteristics of the studied cohorts at hospital admission*

Characteristic	Overall study population N=2069	Diabetes N=448	No diabetesN=1621	p-value
Age, mean (SD), years	67.8 (15.7)	71.7 (11.9)	66.6 (16.3)	<0.001
Age, median (P25, P75), years	69.0 (57.0, 80.0)	72.0 (64.0; 80.0)	67.0 (55.0; 79.0)	<0.001
Sex (male), n (%)	1205 (60.3)	304 (67.9)	950 (58.6)	<0.001
Glucose, mean, (SD) mg/dL mmol/L	 124 (47.7) 6.8(2.6)	 168 (74.4) 9.3 (4.1)	 112 (24.8) 6.2 (1.4)	<0.001
Comorbidities, n (%)				
Hypertension	651 (31.5)	224 (50.0)	427 (26.3)	<0.001
Hyperlipidaemia	409 (19.8)	154 (34.4)	255 (15.7)	<0.001
Obesity	117 (5.65)	45 (10.0)	72 (4.44)	<0.001
Cardiovascular diseases	77 (3.72)	28 (6.25)	49 (3.02)	0.002
Heart failure	51 (2.46)	18 (4.02)	33 (2.04)	0.026
Cerebrovascular diseases	27 (1.30)	10 (2.23)	17 (1.05)	0.086
Ischemic heart disease	47 (2.27)	18 (4.02)	29 (1.79)	0.009
Chronic kidney disease	76 (3.67)	30 (6.70)	46 (2.84)	<0.001
Chronic obstructive pulmonary disease	112 (5.41)	34 (7.59)	78 (4.81)	0.029
Asthma	2 (0.10)	0 (0.00)	2 (0.12)	1.000
Mental disorders	114 (5.51)	35 (7.81)	79 (4.87)	0.022
Cancer	117 (5.65)	36 (8.04)	81 (5.00)	0.019
Pharmacological therapy, n (%)				
Biguanides	66 (3.19)	66 (14.7)	0 (0.00)	<0.001
Sulfonylureas	1 (0.05)	1 (0.22)	0 (0.00)	0.217
Dipeptidyl peptidase 4 inhibitors	11 (0.53)	11 (2.46)	0 (0.00)	<0.001
Fast-acting insulins	95 (4.5)	66 (14.7)	29 (1.79)	<0.001
Intermediate-acting insulins	9 (0.43)	7 (1.56)	2 (0.12)	0.001
Long-acting insulins	23 (1.11)	20 (4.46)	3 (0.19)	<0.001
Antibiotics	1882 (91.0)	421 (94.0)	1461 (90.1)	0.016
Antithrombotics	1752 (84.7)	396 (88.4)	1356 (83.7)	0.017
Renin-angiotensin system agents	523 (25.3)	153 (34.2)	370 (22.8)	<0.001
Beta blocking agents	316 (15.3)	104 (23.2)	212 (13.1)	<0.001
Calcium channel blockers	384 (18.6)	118 (26.3)	266 (16.4)	<0.001
Diuretics	508 (24.6)	185 (41.3)	323 (19.9)	<0.001
Statins	256 (12.4)	88 (19.6)	168 (10.4)	<0.001
Systemic corticosteroids	977 (47.2)	267 (59.6)	710 (43.8)	<0.001
Tocilizumab	421 (20.3)	137 (30.6)	284 (17.5)	<0.001

DM, diabetes mellitus; P25, P75, 25th and 75th percentile, respectively; SD, standard deviation

Figure legend/caption

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Figure 1. Flowchart diagram

Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death or invasive mechanical ventilation.

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

Figure 4. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes (A) and without diabetes (B).

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

Figure 5. Spline plot demonstrating a marked non-linearity in the relationship between plasma glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive mechanical ventilation (IMV) rate (B). Tick marks above the horizontal axis indicate the values at which the observations were made. The dotted lines represent the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD.

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

Figure 6. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized smoothing splines. The shaded area represents the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

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Supplement figure legend/caption

Supplementary Figure 1. Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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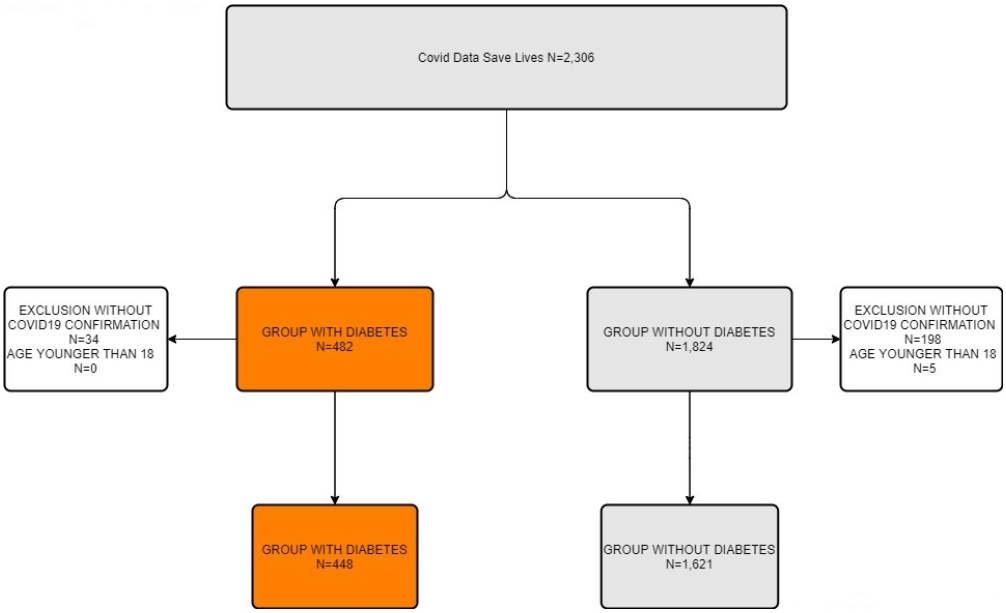

Figure 1. Flowchart diagram

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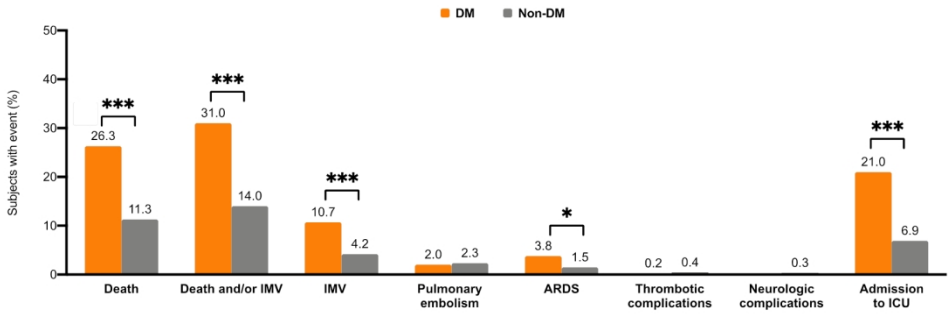

Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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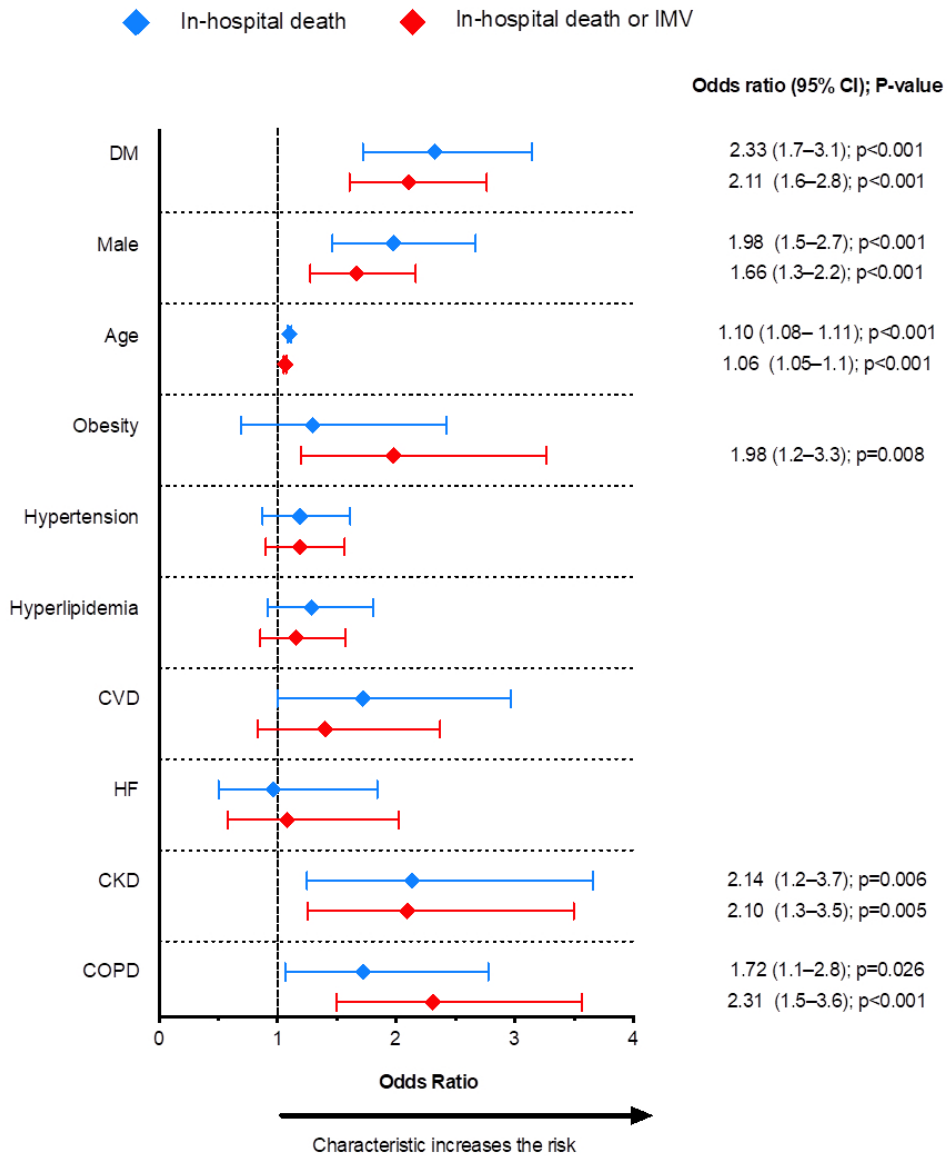

Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death or invasive mechanical ventilation.

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

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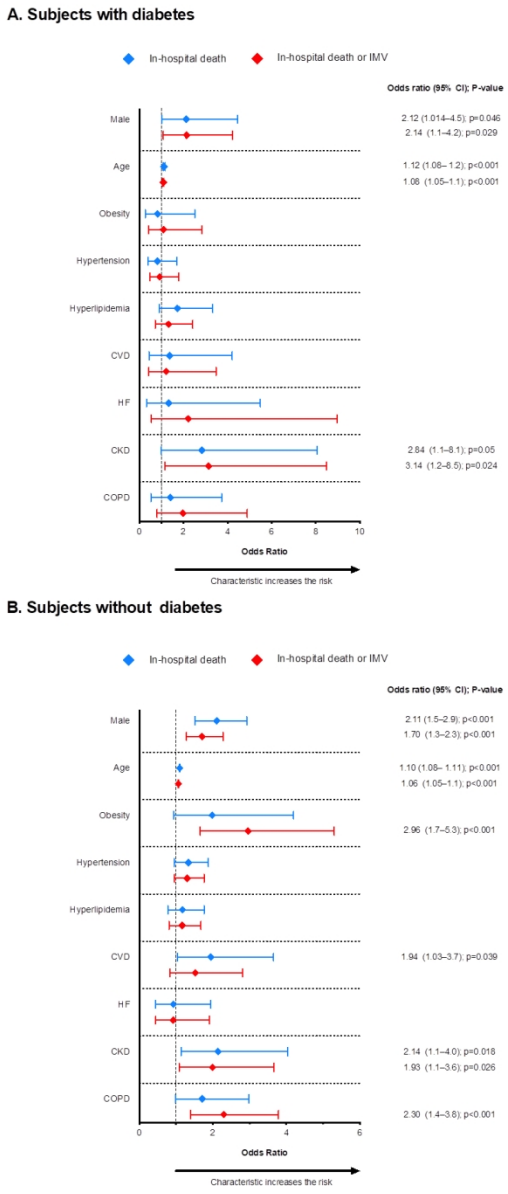

Figure 4. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes (A) and without diabetes (B).

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

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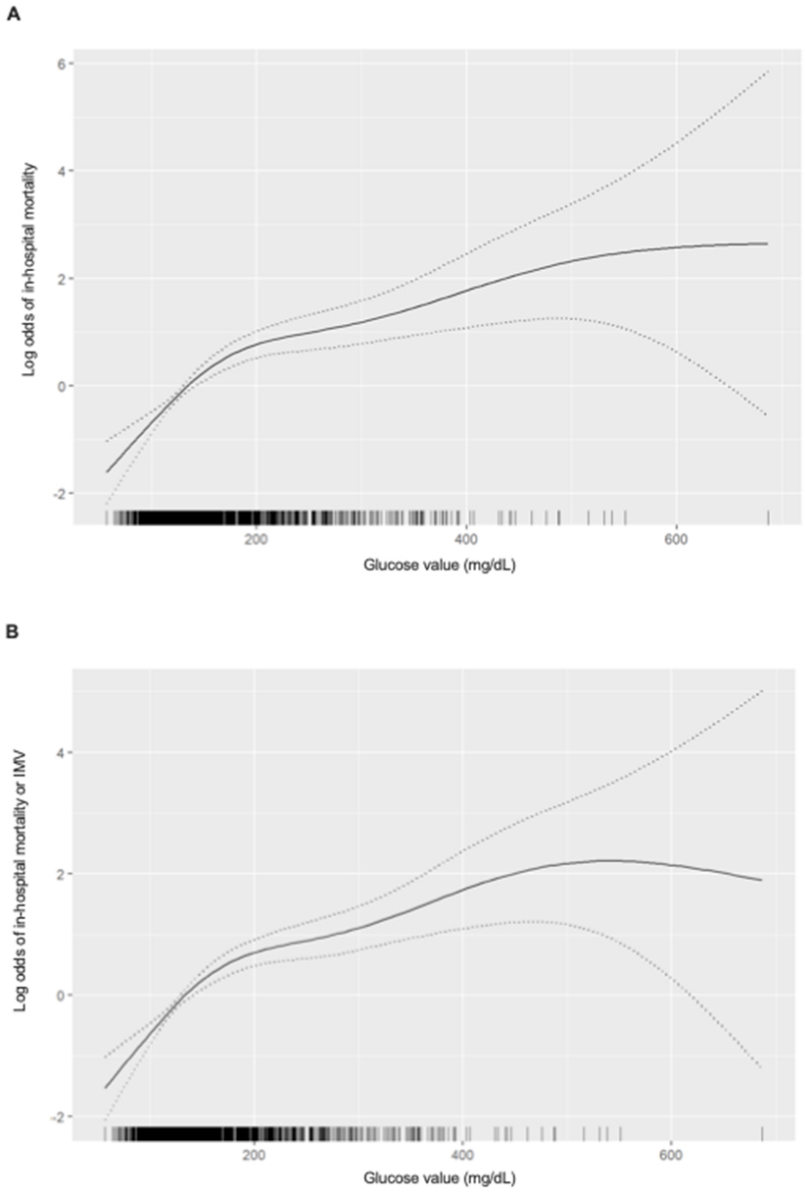

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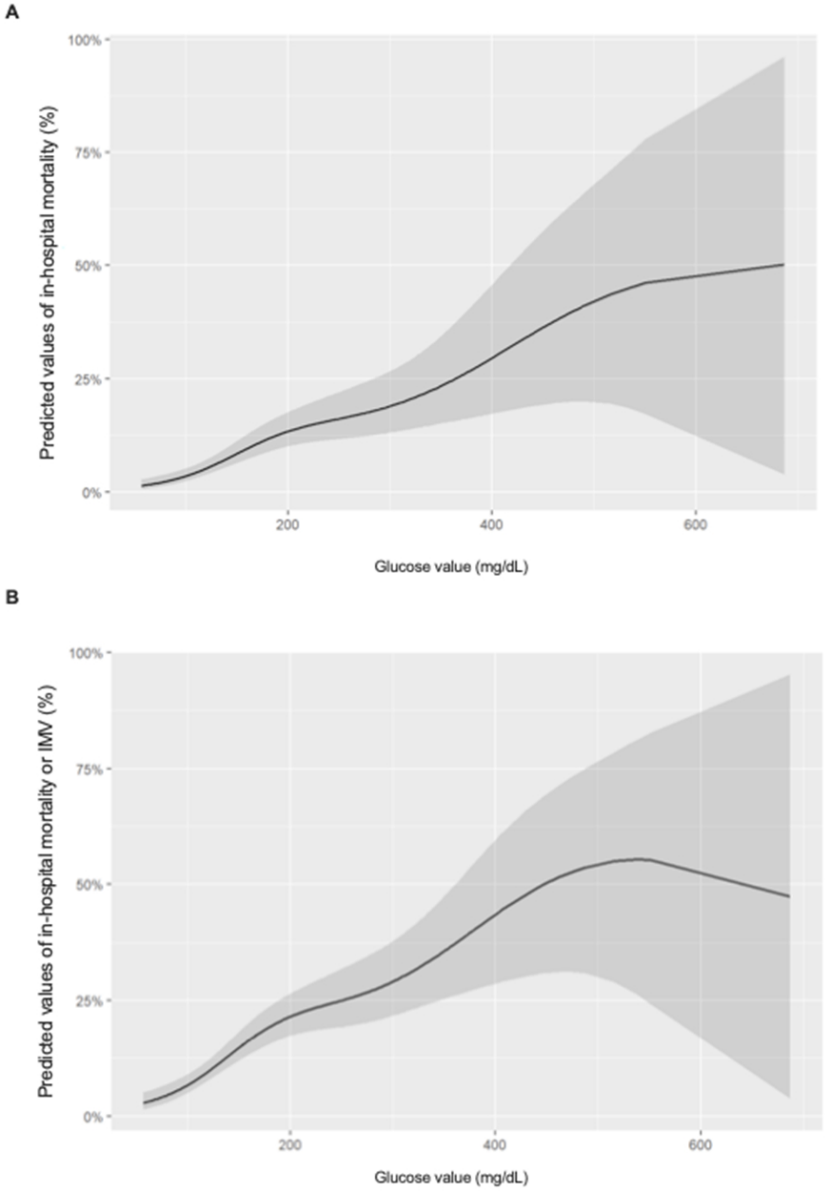
Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

219x323mm (96 x 96 DPI)



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Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

231x333mm (96 x 96 DPI)

ONLINE-ONLY SUPPLEMENTARY MATERIALS

These supplemental materials have been provided by the authors to give the readers additional information about the study.

Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

Emilio Ortega [1,2,3], Rosa Corcoy [4,5,6], Mònica Gratacòs[1], Xavier Cos-Claramunt [1,7], Manel Mata-Cases [1,8,10], Ramon Puig- Treserra[1], Jordi Real [1], Bogdan Vlacho [1], Esmeralda Castelblanco [1,8], Pere Domingo [9], Kamlesh Khunti [11], Josep Franch-Nadal [1,8,12]* and Dídac Mauricio [1,4,8,13]*

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Supplementary Table 1. Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus

	Diabetes N=448	**No diabetes N=1621**	p-value
Vital signs			
Systolic blood arterial pressure, mean (SD), mmHg	128 (19.7)	123 (19.3)	0.037
Diastolic blood arterial pressure, mean (SD), mmHg	72.0 (12.1)	71.1 (12.5)	0.501
Heart rate, mean (SD), bpm	80.2 (14.7)	79.4 (14.9)	0.641
Temperature, mean (SD), °C	36.5 (0.823)	36.5 (0.805)	0.086
Basal laboratory measurements			
Renal function			
Glomerular filtration (CKD-EPI), mean (SD), mL/min/1.73 m²	73.5 (26.5)	81.2 (23.9)	<0.001
Creatinine, mean (SD), mg/dL	1.09 (0.716)	0.943 (0.510)	<0.001
Inflammation markers			
Procalcitonin, mean (SD), ng/mL	0.661 (1.30)	0.387 (1.30)	<0.001
C-reactive protein, mean (SD), mg/L	97.1 (107)	75.9 (82.5)	<0.001
Other biochemical markers			
D-dimer, mean (SD), ng/mL	3990 (10800)	2340 (6720)	<0.001
Liver function			
Alkaline phosphatase, mean (SD), U/L	78.3 (39.1)	78.6 (62.3)	0.984
Lactate dehydrogenase, mean (SD), U/L	644 (399)	575 (311)	<0.001
Gamma-glutamyl transferase, mean (SD), U/L	93.8 (135)	88.4 (123)	0.804
Aspartate aminotransferase, mean (SD), U/L	49.6 (165)	42.7 (57.8)	0.022
Alanine aminotransferase, mean (SD), U/L	51.7 (136)	45.1 (60.6)	0.354
Haematology parameters			
Haemoglobin, mean, (SD), g/dL	13.1 (2.09)	13.6 (1.84)	0.433
Leucocytes, mean (SD), x10³/µL	8.91 (6.52)	7.47 (4.17)	<0.001
Platelets, mean (SD), x10³/µL	247 (112)	250 (116)	0.705

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Monocytes, mean (SD), %	7.21 (5.29)	8.19 (3.91)	<0.001
Lymphocytes, mean (SD), %	15.6 (10.0)	19.0 (10.9)	<0.001
Neutrophils, mean (SD), %	76.1 (13.5)	71.8 (13.5)	<0.001
Prothrombin time, mean (SD), s	15.6 (15.6)	14.8 (10.5)	0.076
Electrolytes			
Phosphorus, mean (SD), mg/dL	3.39 (0.971)	3.15 (0.731)	0.026
Sodium, mean (SD), mg/dL	138 (6.41)	138 (4.35)	0.537
Calcium, mean (SD), mg/dL	8.31 (0.648)	8.39 (0.574)	0.102
Blood gases			
CO_2 pressure, mean (SD), mmHg	37.8 (9.95)	35.8 (7.42)	0.007
O_2 pressure , mean (SD), mmHg	73.4 (35.4)	67.5 (30.9)	0.216
O_2 saturation, mean (SD), %	90.3 (11.4)	89.1 (13.6)	0.694

CKD-EPI, Glomerular filtration rate estimate based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

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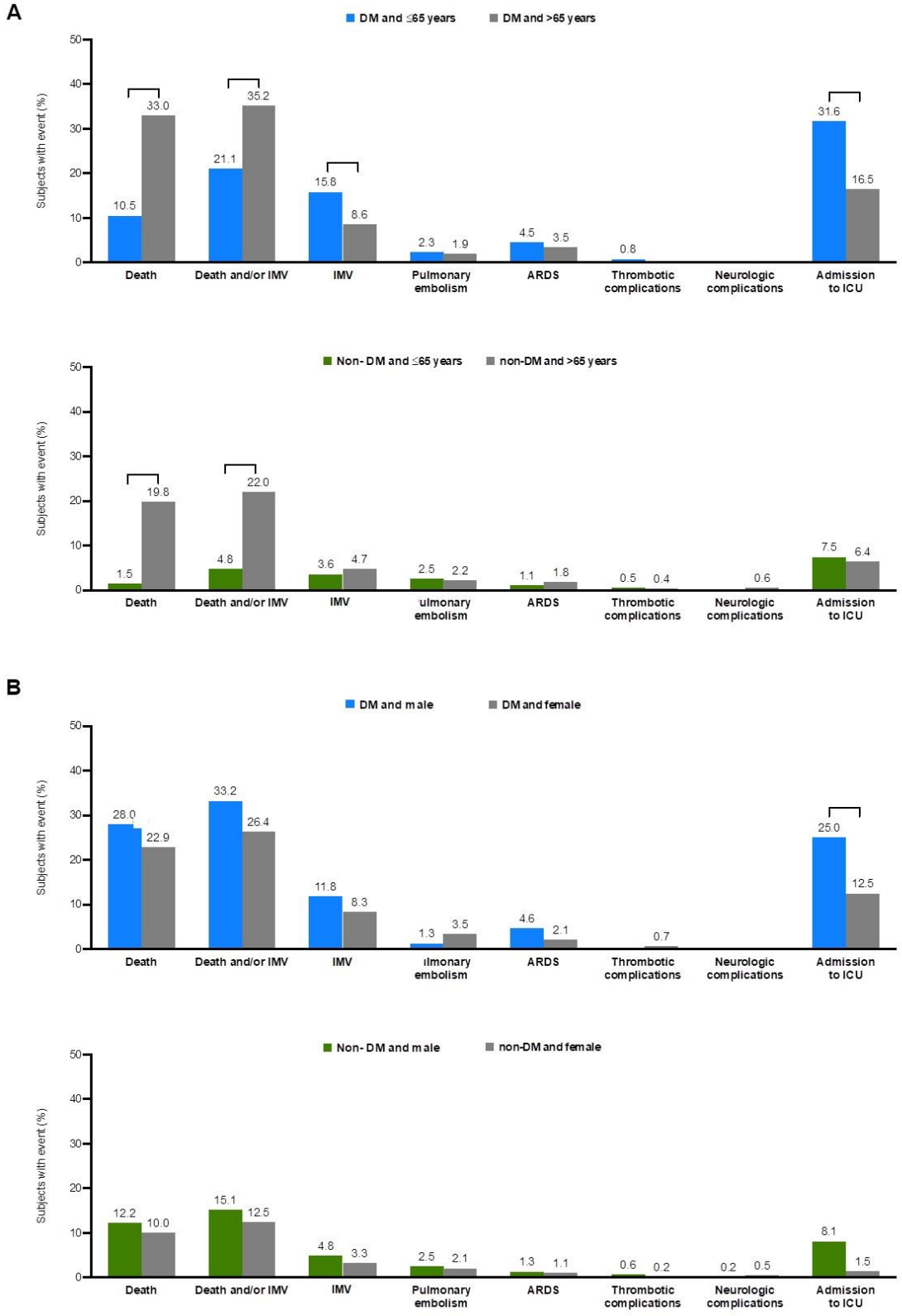
Supplementary Figure 1. Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).



ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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Supplementary table 2. Number of events in patients with pre-existing diabetes and stress hyperglycaemia/unknown diabetes

	Pre-existing diabetes (DM codes and/or HbA1c≥6.5% and/or antidiabetic treatment N=302	Stress hyperglycaemia/unknown diabetes glucose≥200 mg/dl or insulin use in the first 24 hours of admission N=146
Death	69 (22.8%)	49 (33.6%)
Death and or invasive mechanical ventilation	79 (26.2%)	60 (41.1%)
Invasive mechanical ventilation	22 (7.28%)	26 (17.8%)
Pulmonary embolism	5 (1.66%)	4 (2.74%)
Acute respiratory distress syndrome (ARDS)	7 (2.32%	10 (6.85%)
Thrombotic complications	1 (0.33%)	0 (0.00%)
Neurologic complications	0 (0.00%)	0 (0.00%)
Admission to intensive care unit	23 (7.62%)	71 (48.6%)

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Supplementary Table 3. Clinical characteristics at baseline as predictors of death vs death or invasive mechanical ventilation according to the model with all potential independent variables included

	Death			Death or invasive mechanical ventilation		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Diabetes (yes)	2.325 ***	1.719–3.144	<0.001	2.107 ***	1.608–2.761	<0.001
Sex (male)	1.977 ***	1.463–2.670	<0.001	1.663 ***	1.276–2.167	<0.001
Age (years)	1.102 ***	1.087–1.117	<0.001	1.063 ***	1.052–1.075	<0.001
Obesity (yes)	1.297	0.694–2.424	0.414	1.978 **	1.198–3.267	0.008
Hypertension (yes)	1.188	0.874–1.613	0.271	1.188	0.902–1.565	0.221
Hyperlipidaemia (yes)	1.289	0.919–1.808	0.141	1.158	0.853–1.572	0.346
Cardiovascular diseases (yes)	1.721	0.999–2.966	0.051	1.403	0.830–2.370	0.206
Heart failure (yes)	0.964	0.504–1.842	0.911	1.082	0.578–2.023	0.806
Chronic renal insufficiency (yes)	2.135 **	1.246–3.659	0.006	2.096 **	1.255–3.498	0.005
COPD (yes)	1.721 *	1.066–2.779	0.026	2.310 ***	1.498– .564	<0.001
Observations	2069			2069		
R2 Tjur	0.208			0.157		
Hosmer–Lemeshow test	0.26			0.94		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 4. Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.

	Death		
Predictors	Odds Ratios	95% CI	p-value
Diabetes * Obesity	0.720	0.214–2.425	0.596
Diabetes * Hyperlipidaemia	0.766	0.407–1.442	0.408
Diabetes * Heart failure	1.406	0.373–5.298	0.614
Diabetes * Chronic kidney disease	0.805	0.273–2.371	0.693
Diabetes * COPD	0.631	0.235–1.696	0.361

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Supplementary Table 5. Clinical characteristics at baseline associated with in-hospital death stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	2.107 ***	1.516–2.929	<0.001	2.125 *	1.014–4.451	0.046
Age	1.096 ***	1.081–1.112	<0.001	1.124 ***	1.081–1.170	<0.001
Obesity	1.984	0.938–4.198	0.073	0.826	0.272–2.511	0.736
Hypertension	1.333	0.947–1.876	0.099	0.823	0.400–1.697	0.598
Hyperlipidaemia	1.173	0.780–1.765	0.443	1.729	0.899–3.326	0.101
Cardiovascular diseases	1.943 *	1.033–3.654	0.039	1.368	0.445–4.208	0.584
Heart failure	0.926	0.442–1.944	0.840	1.330	0.323–5.484	0.693
Chronic kidney disease	2.143 *	1.137–4.038	0.018	2.839 *	1.000–8.060	0.050
COPD	1.712	0.984–2.979	0.057	1.404	0.529–3.729	0.495
Observations	1795			274		
R2 Tjur	0.178			0.240		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 6. Clinical characteristics at baseline associated to in-hospital death or mechanical ventilation stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	1.710 ***	1.282–2.280	<0.001	2.138 *	1.081–4.226	0.029
Age	1.061 ***	1.050–1.073	<0.001	1.082 ***	1.047–1.118	<0.001
Obesity	2.958 ***	1.651–5.298	<0.001	1.090	0.420–2.827	0.860
Hypertension	1.297	0.955–1.762	0.096	0.920	0.473–1.789	0.806
Hyperlipidaemia	1.165	0.811–1.675	0.408	1.326	0.728–2.415	0.356
Cardiovascular diseases	1.525	0.827–2.814	0.177	1.217	0.426–3.477	0.714
Heart failure	0.923	0.447–1.906	0.829	2.219	0.549–8.971	0.264
Chronic kidney disease	1.993 *	1.084–3.662	0.026	3.140 *	1.163–8.474	0.024
COPD	2.298 **	1.396–3.781	0.001	1.976	0.800–4.885	0.140
Observations	1795			274		
R2 Tjur	0.129			0.190		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 7. Multivariate model of the association between predictors and the odds of death and death or invasive mechanical ventilation based on the nonlinear glucose curve.

	Death			Death or Invasive mechanical ventilation		
Predictors	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Sex (male)	1.911 ***	1.375–2.655	<0.001	1.540 **	1.159–2.047	0.003
Age	1.108 ***	1.090–1.125	<0.001	1.062 ***	1.049–1.074	<0.001
Obesity	1.079	0.527–2.206	0.836	1.814 *	1.057–3.112	0.031
Hypertension	1.109	0.800–1.537	0.534	1.134	0.849–1.515	0.394
Hyperlipidaemia	1.330	0.928–1.906	0.120	1.152	0.837–1.585	0.386
Cardiovascular diseases	1.686	0.958–2.967	0.070	1.356	0.792–2.325	0.267
Heart failure	0.768	0.388–1.520	0.448	0.911	0.472–1.757	0.781
Chronic kidney disease	2.251 **	1.268–3.996	0.006	2.151 **	1.250–3.701	0.006
COPD	1.666 *	1.006–2.760	0.047	2.253 ***	1.436–3.536	<0.001
Observations			1877			1877
R2			0.241			0.188

p<0.05 ** p<0.01 *** p<0.001

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Covid Data Save Lives

HM Hospitales makes an anonymous dataset freely available to the international medical and scientific community with all the available clinical information on patients treated in our hospital centers for the SARS-CoV-2 virus

Compared to most of the existing **databases on COVID-19,** focused on demographic data, this clinical dataset collects the different interactions in the **COVID-19 treatment process, including detailed information on diagnoses, treatments, admissions, ICU admissions, diagnostic imaging tests, laboratory results, discharge or death, among many other records.**
With the opening of this dataset, we intend to take the first step and serve as an example for other institutions to be encouraged to share their information and thus, together, be able to offer the medical and scientific community clinical data with which to obtain predictive models of evolution, epidemiological models, information on the response to the various treatments applied, **knowledge of virus for the creation of a vaccine, and sociodemographic data on the impact on the population of the virus.**

Dataset “Covid Data Save lives”

The information in this data set comes from the HM Hospitales EHR system. It contains the anonymized records of 2,310 patients, admitted with a diagnosis of COVID POSITIVE or COVID PENDING, since the beginning of the epidemic to date. The information is organized in tables according to their content, all of them linked by a unique admission identifier. This identifier is the de-anonymization key, explicitly created for this purpose, and has nothing to do with the actual identifier of each admission.

- The main table includes data on the admission and the patient (age and sex), data on the previous emergency if there has been one (2,226 records), data on their stay in the ICU if there has been one and records of the first and last set of emergency constants.
- The medication table shows all the medication administered to each patient during admission (more than 60,000 records), with the dates

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corresponding to the first and last administration of each drug, identified by their brand name and classification in the ATC5/ATC7.

- In the table of vital signs, there are all the basic records of constants (54,000 records so far) collected during admission with their date and time of registration.
- The laboratory table contains the results of the determinations (398,884 records) of all the requests made to each patient during admission and in the previous emergency, if any.
- And finally, the ICD10 coding tables show the records of diagnostic and procedural information coded according to the international ICD10 classification in its latest distributed version (does not include COVID), for the patients referred, both for episodes of hospital admission (more than 1,600) and for the emergency (more than 1,900) prior to those episodes, if any.

Web page: https://www.hmhospitales.com/coronavirus/covid-data-save-lives/english-version

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

Emilio Ortega, Rosa Corcoy,Mònica Gratacòs, Xavier Cos-Claramunt , Manel Mata-Cases , Ramon Puig- Treserra, Jordi Real , Bogdan Vlacho , Esmeralda Castelblanco , Pere Domingo , Kamlesh Khunti , Josep Franch-Nadal and Dídac Mauricio

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	**Abstract**
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			**Page 4-5 Lines: 2-24 and 1-22**
Objectives	3	State specific objectives, including any prespecified hypotheses			**Page 6 Lines: 4**
Methods					

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Study Design	4	Present key elements of study design early in the paper			**Page 7 Lines: 3-4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			**Page 7 Lines:4-11**
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	**Page 7 Lines:19-24 Page 8 Lines:1-4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	**Page 8 Lines:5-14**

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Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			**Page 7 Lines:12-16**
Bias	9	Describe any efforts to address potential sources of bias			**Page 9 Lines:1-7**
Study size	10	Explain how the study size was arrived at			**NA**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			**Page 8 Lines:21-24**
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity			**Page 8 Lines:21-24 Page 9 Lines: 1-12**

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		analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	**Page 7 Lines:12-18**
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	**NA**
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	**Page 9 Lines:18-24**
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data			**Page 10 Lines:1-11**

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		for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			**Page 10** **Lines: 12-19**
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			**Page 10** **Lines:20-25** **Page 11** **Lines: 1-23** **Page 12** **Lines:1-4**
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			**Page 12** **Lines5-17**
Discussion					
Key results	18	Summarise key results with reference to study objectives			**Page 12** **Lines: 19-24**
Limitations	19	Discuss limitations of the study,		RECORD 19.1: Discuss the	**Page 14**

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		taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	**Lines:22-24 Page 15 Lines:1-22**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			**Page 13 Lines:1-22 Page 14 Lines: 1-20**
Generalisability	21	Discuss the generalisability (external validity) of the study results			**Page 16 Lines:1-10**
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			**Page 17 Lines: 11**
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	**Page 17 Lines:12-13**

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*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

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Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

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Abstract:

Aim: This study's objective was to assess the risk of severe in-hospital complications of patients admitted for coronavirus disease (COVID-19) and diabetes mellitus (DM).

Design: This was a cross-sectional study

Settings: We used pseudonymised medical record data provided by six general hospitals from the HM Hospitales group in Spain.

Outcome measures: Multiple logistic regression analyses were used to identify variables associated with mortality and the composite of mortality or invasive mechanical ventilation (IMV) in the overall population, and stratified for the presence or absence of DM. Spline analysis was conducted on the entire population to investigate the relationship between glucose levels at admission and outcomes**.**

Results: Overall, 1,621 individuals without DM and 448 with DM were identified in the database. DM patients were on average 5.1 years older than those without. The overall in-hospital mortality was 18.6% (N=301), and was higher among patients with DM than without (26.3% *vs.* 11.3%; p<0.001). DM was independently associated with death, and death or IMV (OR=2.33, 95% CI: 1.7–3.1 and OR=2.11, 95% CI: 1.6– 2.8, respectively; p<0.001). In DM subjects, the only variables independently associated with both outcomes were age >65 years, male sex, and pre-existing chronic kidney disease (CKD). We observed a non-linear relationship between blood glucose levels at admission and risk of in-hospital mortality and death or IMV. The highest probability for each outcome (around 50%) was at random glucose of around 550 mg/dL (30.6 mmol/L), the risks flattened above this value.

Conclusion: The results confirm the high burden associated with DM in patients hospitalized with COVID-19 infection, particularly among males, the elderly, and those with impaired kidney

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function. Moreover, hyperglycaemia on admission was strongly associated with poor outcomes, suggesting that personalised optimisation could help to improve outcome during the hospital stay.

Keywords: COVID-19**,** Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation

Strengths and limitations of this study

- A major strength of our study is the thorough methodological approach to analyse the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia.
- We were limited by not having access to the patients' medical history prior to admission, and the low number of registers for some important DM variables (such as Hb1Ac), and the lack of data on weight or BMI (only the presence of obesity).
- The selection of DM subjects was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose levels at admission.
- We used random blood glucose on admission for spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.

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1. Introduction

On January 30, 2020, the World Health Organization (WHO) declared the outbreak of the novel SARS-CoV-2 coronavirus pandemic, a public health emergency of international importance. A few days later, the respiratory disease caused by SARS-CoV-2 was officially named COVID-19 (Corona Virus Infectious Disease 2019) [1, 2]. The first person diagnosed as positive in Spain was confirmed on January 31, 2020, on the island of La Gomera [3]. The median age of hospitalized patients infected with SARS-CoV-2 is 46.2 years, men comprise about 60% of patients, and the average incubation period is 5.7 days [4]. As of February 8, 2021, approximately 3 million people have been infected with SARS-CoV-2 in Spain since the start of the COVID-19 pandemic, and 62,295 persons have died.

Several meta-analyses have reported that the most severe and fatal cases of COVID-19 occur among the elderly and in patients with underlying comorbidities [5-7]. Indeed, those with two or more concomitant diseases have a significantly higher risk of admission to an intensive care unit (ICU), invasive ventilation, or death compared with those with a single concomitant disease, or without comorbidities [8]. The most prevalent comorbidities associated with increased COVID-19-related morbidity and mortality are the presence of diabetes mellitus (DM), cardiovascular diseases (CVDs), chronic lung disease, chronic kidney disease (CKD), hypertension, cancer, and obesity [5-7]. 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].

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

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with the cellular membrane [10]. Although it was initially assumed that ACE inhibitors and angiotensin receptor blockers to treat hypertension or cardiovascular conditions 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.

Previous studies have reported that people with DM are prone to new infections and recurrence, particularly influenza and pneumonia, due to impaired defences and disease complications [13-16]. Although the estimated prevalence of DM in COVID-19 infected patients varies greatly by geographical region, it is considered similar to the DM prevalence in the general population, thus not representing a risk factor for infection [17]. However, the prevalence of diabetes among COVID-19 hospitalized subjects is higher than the overall diabetes prevalence [17, 18]. A study conducted in England found that a third of in-hospital deaths occurred in people with type 2 DM and that these patients had greater odds of COVID-19-related in-hospital death than those without DM [19]. This observation has been confirmed in a meta-analysis showing that DM is associated with a 2-fold higher risk of dying from COVID-19 [20], and a second study reporting that patients with pre-existing DM have a 3-fold greater risk of in-hospital mortality [21].

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].

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In Spain, DM is a highly prevalent disease in people over 18 years of age (13.8% of the population) [27]. Given the high prevalence of DM and the additional challenging scenario that COVID-19 poses to health care professionals in this particular population, it is crucial to accumulate and share information and data from different countries and regions [28]. Following this notion, the main objective of this study was to assess the risk of in-hospital COVID-19-related complications based on the presence of DM or overt hyperglycaemia at admission in Spain.

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2. Methods

2.1 Study design and settings

This was a cross-sectional study in hospitalized individuals infected with SARS-CoV-2, stratified by presence or absence of DM. Data were obtained from pseudonymized electronic health records provided by six general hospitals from the HM Hospitales group (Spain). 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 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. Detailed information related to the database is presented in the Supplementary material (**Database description**). The REporting of studies Conducted using Observational Routinely-collected Data (RECORD) Checklist is presented as Supplementary material.

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.

2.2 Inclusion and Exclusion Criteria

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

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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.

2.3 Study Variables

The following baseline variables were collected: age and sex; SARS-CoV-2 diagnosis (positive RT-PCR); comorbidities (i.e., hypertension, hyperlipidaemia, obesity [BMI ≥30 kg/m^2], CVD, heart failure, cerebrovascular diseases, ischemic heart disease, CKD, chronic obstructive pulmonary disease [COPD], asthma, mental disorders, and cancer); blood laboratory parameters (i.e., HbA1c, BG, electrolytes, renal function, liver function, haematology and coagulation, inflammation markers, and gas tests); clinical parameters (i.e., systolic and diastolic blood pressure, heart rate, and temperature), and concomitant medications (i.e., baseline insulins, systemic corticosteroids, antimicrobials, anticoagulants and antiplatelet agents, and antihypertensive and lipid-lowering drugs).

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

2.4 Statistical Methods

The demographic and clinical characteristics of the two groups of hospitalized patients (i.e., with or without DM) were compared and summarized at the quantitative (minimum, maximum, median, first and third quartile, mean, and standard deviation [±SD]) or categorical level (frequency, number and %).

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The association between the study outcomes (i.e., mortality and mortality or mechanical ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and associated risk factors. 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 the respective 95% confidence intervals (CI). We evaluated goodness of fit of the logistic regression models with H&L test (Hosmer–Lemeshow test). To analyse the nonlinear relationship of random blood glucose levels on admission with the two study outcomes, we used an adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves with two degrees of freedom (knots) using the mgcv package in R, version 1.8-31[29] with adjustment for potential confounders. We analysed the entire database available and no statistical power was calculated. Data management and statistical analyses were performed using the R statistical software version 3.6.1 (https://www.r-project.org/).

2.5 Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

3.1. Baseline Characteristics

Of the 2,306 subjects admitted to hospital within the period of study, 2,069 were over 18 years of age and had a positive diagnostic test for SARS-CoV-2 (**Figure 1**). Among them, 448 (21.7%) were identified as having DM and 1,621(78.3%) without DM (non-DM group). The characteristics of the two populations at hospital admission are shown in **Table 1**. Subjects with DM were on average 5.1 years older than non-DM subjects, and more frequently male (67.9% *vs.* 58.6%). Moreover,

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individuals in the DM group had a poor comorbidity profile, with a higher frequency of all assessed prior conditions except for cerebrovascular diseases and asthma.

Regarding laboratory parameters on admission (**Supplementary Table 1)**, the DM group had slightly lower estimated glomerular filtration rates (eGFR) (73.5±26.5 mL/min/1.73 m^2 *vs.* 81.2±23.9 mL/min/1.73 m^2; p<0.001), and higher levels of serum creatinine (1.09±0.72 mg/dL *vs.* 0.94±0.51 mg/dL; p<0.001) than the non-DM group. Regarding markers of inflammation and infection, we observed higher levels of C-reactive protein and procalcitonin in the DM group (97.1±107 mg/L *vs.* 75.9± 82.5 mg/L and 0.66±1.30 mg/L *vs.* 0.39±1.30 mg/L, respectively; p<0.001). We also observed higher levels of D-dimer, a marker of endothelial and coagulation dysfunction in the DM group (3990 ±10800 ng/mL *vs* .2340 ±6720 ng/mL, respectively). 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.

3.2 Events and complications during in-hospital stay

A total of 301 (14.5%) subjects positive for SARS-CoV-2 died in-hospital, 118 (26.3%) out of 448 in the DM group and 183 (11.3%) out of 1621 in the non-DM group (p<0.001; **Figure 2**). All studied events, except pulmonary embolism and thrombotic or neurologic complications, were significantly more frequent among patients with DM than without (**Figure 2**). The most frequent outcome was the composite of death or IMV (31% in the DM group *vs.* 14% in the non-DM group; **Figure 2**) 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%).

The frequency of events by group and age showed that, in both subjects with and without DM, death and the composite of death or IMV were significantly more frequent among those >65 years (**Supplementary Figure 1**). In contrast, the proportion of subjects requiring IMV and ICU admission

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was significantly higher among those ≤65 years and with DM, while age was not significant in those without DM. 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**). 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.**

3.3. Baseline demographic and clinical characteristics associated with in-hospital death and death or IMV

For the overall hospitalized population, the demographic characteristics significantly associated with mortality were male sex and older age (OR=1.98, 95% CI=1.2–3.3 and OR=1.10, 95% CI=1.08–1.11, respectively) (**Figure 3; Supplementary Table 3**). The comorbidities independently associated with increased odds of death were DM (OR=2.33, 95% CI=1.7–3.1), CKD (OR=2.14, 95% CI=1.2–3.7), and COPD (OR=1.72, 95% CI=1.1–2.8).

When considering the composite outcome of death or IMV, the same variables associated with death (i.e., age, sex, diabetes, CKD, and COPD) were identified as increasing the risk. In addition, obesity emerged as an independently associated variable (OR=1.98, 95% CI=1.5–2.7) (**Figure 3**, **Supplementary Table 3).**

The multiple logistic regression models were repeated to rule out the potential interaction of DM with different clinical conditions (i.e., obesity, hyperlipidaemia, obesity and hyperlipidaemia, heart failure, CKD, and COPD) for the in-hospital death outcome. The results showed that none of these conditions affected the relationship between the risk of death and DM (**Supplementary Table 4**).

3.4. Factors associated with hospital death and death or IMV by comorbid diabetes

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A sub-analysis was performed separately for subjects with or without DM. In the DM group, the only variables independently associated with the risk of both mortality and death or IMV were male sex, older age, and CKD (**Figure 4A** and **Supplementary Table 5** and **6**). In contrast, in subjects without DM, besides the aforementioned variables, the odds of death were also increased among subjects with CVD (OR=1.94, 95% CI=1.03– 3.7), and the odds of death or IMV among those with obesity or COPD (OR=2.96, 95% CI=1.7–5.3 and OR=2.30, 95% CI= 1.4 – 3.8, respectively) (**Figure 4B** and **Supplementary Table 5** and **6)**.

3.5. Factors associated with hospital death and death or IMV by glucose levels at admission

We used non-parametric logistic regression models to assess whether there was a relationship between random BG on admission and the risk of mortality (and death or IMV). We observed a marked non-linearity in the effect of BG on admission in the risk of both outcomes (**Figure 5A and 5B** and **Supplementary Table 7**). While the risk was increased among subjects with high random BG levels on admission, the magnitudes of the associated mortality differed depending on the baseline values, with a large increase in the log-odds of death or IMV with values up to 200 mg/dL (11.1 mmol/L), and smaller increases above this level. The logistic regression models (**Figure 6A and 6B**) showed that the highest probability of death (near 50%) was at around 550 mg/dL (30.6 mmol/L) and, above this value, the mortality risk flattened. Finally, the multivariate model showed that, beside glucose at admission, male sex, older age, CKD, and COPD were associated with in-hospital death (**Supplementary Table 7**). These variables were linked to death or IMV too, but obesity was an additional risk factor (**Supplementary Table 7**).

4. Discussion

Data from this cross-sectional study showed that the COVID-19 related in-hospital death rate was higher among subjects with DM than without. Moreover, DM was independently associated with the risk of in-hospital case fatality and the composite outcome, death or IMV. In the DM group,

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both outcomes were associated with older age, male sex, and pre-existing CKD. Finally, we observed a non-linear relationship between BG levels on admission and the probability of death and death or IMV in the overall inpatient population.

In our study, the proportion of severe COVID-19 cases (e.g., requiring IMV or ICU admission) in the DM population was higher than in the non-DM cohort. Moreover, DM patients were more frequently male and over 65 years, had more comorbid conditions, and higher levels of inflammatory, endothelial, and coagulation dysfunction markers on admission. Different meta-analyses have reported that older age and male sex are characteristics associated with severe COVID-19 infection and high fatality rates [17, 30, 31]. Along the same line, studies assessing the phenotypic characteristics of COVID-19 patients with pre-existing DM have found that those with severe infection were older, had more comorbidities (i.e., cerebrovascular disease, CVD, hypertension, and COPD), and increased values of inflammation, endothelial and coagulation dysfunction markers (e.g., D-dimer, procalcitonin, and thrombocytopenia), than those without DM [30- 35].

In our study, patients with DM had significantly higher creatinine on admission, lower eGFR, and more frequently pre-existing CKD than non-DM subjects. Besides, CKD was the only comorbid condition increasing the odds (three-fold increase) of in-hospital death (and death or IMV) among the DM cohort after adjusting for age, sex, and confounding variables. Different meta-analyses have identified CKD as a risk factor for severity and in-hospital death in SARS-CoV-2 infected patients [7, 36 -38]. 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 [39]. Although it is difficult to distinguish whether poor outcomes are linked to acute kidney injury (AKI) developed during the course of the disease, or to pre-existing CKD [39], a study conducted in Spain showed that patients with increased creatinine on admission, previous CKD, or

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developing AKI, had a higher risk of in-hospital death than those with normal creatinine on admission [40]. Of note, the authors found that older age and diabetes, but not other comorbidities, were associated with in-hospital death [40]. Finally, a study conducted in Mexico reported that, patients with DM and CKD had a 2-fold higher rate of intubation, 56% higher ICU admission, and 21% excess probability of case-fatality once admitted, than subjects with CKD alone [41].

In our study, we used splines as a scientific and preferable alternative to the categorization of BG levels [42]. We used this approach because a recent dose-response meta-analysis demonstrated a non-linear relationship between admission fasting blood glucose (FBG) level and COVID-19 severity, with high levels being significantly associated with increased mortality and poor outcome, regardless of pre-existing DM [43]. These results confirmed previous observations that FBG on admission, and the odds of being admitted to the ICU, followed a logarithmic association, with different magnitudes of risk depending on the baseline level [42]. We add to the literature that, besides the previously reported effect of hyperglycaemia on the risk of COVID-19 severity, ICU admission, and mortality [24,25], BG has a non-linear relationship with case fatality and the risk of death or IMV. It is possible that this relationship was also accompanied by, or reflected glycaemic variability and less time spent in range. Indeed, glycaemic fluctuation has been reported to be independently associated with poor prognosis and mortality in COVID-19 hospitalized patients [44]. In the same vein, a study on ICU patients showed that the less time spent in range was associated with increased utilization of a ventilator, prolonged mechanical ventilation, and increased mortality [45]. Most importantly, a spline analysis of glucose levels in DM patients with continuous glucose monitoring showed a non-linear relationship between time spent above range and glycaemic variability with the increased likelihood of composite adverse COVID-19 outcomes (need for ICU admission, mechanical ventilation, or critical illness) [46].

4.1 Limitations of this study

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The findings of this study must be interpreted with caution and a number of limitations should be borne in mind. Firstly, we had limited data for SARS-CoV-2 infected persons. For instance, we did not have access to the patient's medical history prior to admission; so the possibility exists that some important medical conditions were not included in the emergency room medical report and, therefore, not included in the analysis. Moreover, data on socio-demographic characteristics (ethnicity, race, economic or educational status) and toxic habits (smoking, alcohol or drug use) were not available. 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 for 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. Thirdly, the selection of subjects with DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose levels), which could have introduced selection or referral bias, potentially leading to an inaccurate estimation of DM prevalence. 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 be also attributed to antidiabetic treatment underreporting at admission. Fourthly, and inherent to data coming from hospital medical records, missing values could have reduced the statistical power of the study, or produced biased estimates. Fifthly, we used random BG on admission for the spline analyses, thus preventing the distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM. This also prevented the analysis of time in range or BG variability, both being linked to increased severity, case fatality, and poor COVID-19 outcomes [42-46]. Lastly, the study period coincides with the height of the first pandemic wave in Spain, when there was a shortage of ventilators and intensive care beds. At this point, age was the deciding factor for whether or not someone received potentially life-saving ICU

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care. This might be reflected in our results, where in-hospital death was more frequent among those over 65 years, but ICU admission was more frequent among those ≤65 years.

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5. Conclusions

The results of our study confirm the high burden associated with DM in patients hospitalized due to SARS-CoV-2 infection. Comorbid DM poses a challenge to health professionals and the system because it is associated with severe disease, higher ICU admission rates, IMV, and ultimately death, particularly among the elderly. The non-linear relationship of hyperglycaemia at admission with increased odds of death and IMV suggests that, optimizing glycaemic control during the hospital stay could help to reduce in-hospital death and the composite death/IMV. Besides, out-of-hospital care should be a priority to reduce or prevent uncontrolled glycaemia among those with DM, as it could potentially help reduce poor outcomes when hospitalization is required.

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Ethics approval: The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol, Barcelona (approval number: 20/089-PCV). This study does not involve animal subjects.

Author Contributions: Conceptualization, E.O, J.F-N, R.C, M.M-C, B.V, K.K, D.M.; methodology, E.O, J.F-N, R.C, M.M-C, B.V, K.K, D.M.; formal analysis, R.P-T and J.R.; resources and data curation, R.P-T, J.R and B.V.; writing—original draft preparation, B.V and M.G.; writing—review and editing, E.O, J.F-N, R.C, M.M-C, M.G, FX.C-C, E.C, B.V, K.K, D.M and P.D.; supervision: D.M, R.C and J.F-N.; project administration: B.V.

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Table 1. *Baseline characteristics of the studied cohorts at hospital admission*

Characteristic	Overall study population N=2069	Diabetes N=448	No diabetes N=1621	p-value
Age, mean (SD), years	67.8 (15.7)	71.7 (11.9)	66.6 (16.3)	<0.001
Age, median (P25, P75), years	69.0 (57.0, 80.0)	72.0 (64.0; 80.0)	67.0 (55.0; 79.0)	<0.001
Sex (male), n (%)	1205 (60.3)	304 (67.9)	950 (58.6)	<0.001
Glucose, mean, (SD) mg/dL mmol/L	 124 (47.7) 6.8(2.6)	 168 (74.4) 9.3 (4.1)	 112 (24.8) 6.2 (1.4)	<0.001
Comorbidities, n (%)				
Hypertension	651 (31.5)	224 (50.0)	427 (26.3)	<0.001
Hyperlipidaemia	409 (19.8)	154 (34.4)	255 (15.7)	<0.001
Obesity	117 (5.65)	45 (10.0)	72 (4.44)	<0.001
Cardiovascular diseases	77 (3.72)	28 (6.25)	49 (3.02)	0.002
Heart failure	51 (2.46)	18 (4.02)	33 (2.04)	0.026
Cerebrovascular diseases	27 (1.30)	10 (2.23)	17 (1.05)	0.086
Ischemic heart disease	47 (2.27)	18 (4.02)	29 (1.79)	0.009
Chronic kidney disease	76 (3.67)	30 (6.70)	46 (2.84)	<0.001
Chronic obstructive pulmonary disease	112 (5.41)	34 (7.59)	78 (4.81)	0.029
Asthma	2 (0.10)	0 (0.00)	2 (0.12)	1.000
Mental disorders	114 (5.51)	35 (7.81)	79 (4.87)	0.022
Cancer	117 (5.65)	36 (8.04)	81 (5.00)	0.019
Pharmacological therapy, n (%)				
Biguanides	66 (3.19)	66 (14.7)	0 (0.00)	<0.001
Sulfonylureas	1 (0.05)	1 (0.22)	0 (0.00)	0.217
Dipeptidyl peptidase 4 inhibitors	11 (0.53)	11 (2.46)	0 (0.00)	<0.001
Fast-acting insulins	95 (4.5)	66 (14.7)	29 (1.79)	<0.001
Intermediate-acting insulins	9 (0.43)	7 (1.56)	2 (0.12)	0.001
Long-acting insulins	23 (1.11)	20 (4.46)	3 (0.19)	<0.001
Antibiotics	1882 (91.0)	421 (94.0)	1461 (90.1)	0.016
Antithrombotics	1752 (84.7)	396 (88.4)	1356 (83.7)	0.017
Renin-angiotensin system agents	523 (25.3)	153 (34.2)	370 (22.8)	<0.001
Beta blocking agents	316 (15.3)	104 (23.2)	212 (13.1)	<0.001
Calcium channel blockers	384 (18.6)	118 (26.3)	266 (16.4)	<0.001
Diuretics	508 (24.6)	185 (41.3)	323 (19.9)	<0.001
Statins	256 (12.4)	88 (19.6)	168 (10.4)	<0.001
Systemic corticosteroids	977 (47.2)	267 (59.6)	710 (43.8)	<0.001
Tocilizumab	421 (20.3)	137 (30.6)	284 (17.5)	<0.001

DM, diabetes mellitus; P25, P75, 25th and 75th percentile, respectively; SD, standard deviation

Figure legend/caption

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Figure 1. Flowchart diagram

Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death or invasive mechanical ventilation.

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

Figure 4. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes (A) and without diabetes (B).

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

Figure 5. Spline plot demonstrating a marked non-linearity in the relationship between plasma glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive mechanical ventilation (IMV) rate (B). Tick marks above the horizontal axis indicate the values at which the observations were made. The dotted lines represent the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD.

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

Figure 6. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized smoothing splines. The shaded area represents the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

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Supplement figure legend/caption

Supplementary Figure 1. Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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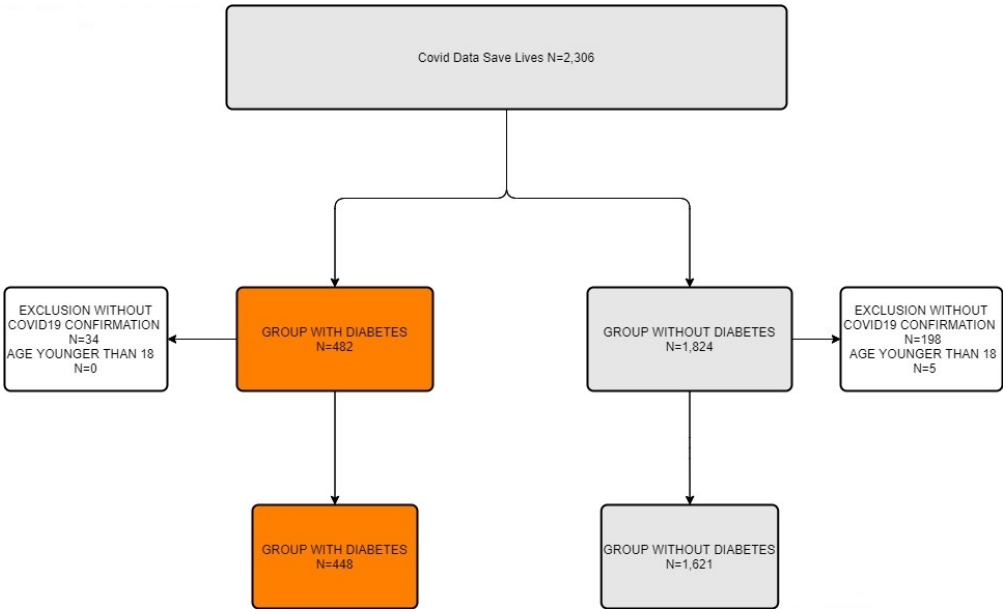

Figure 1. Flowchart diagram

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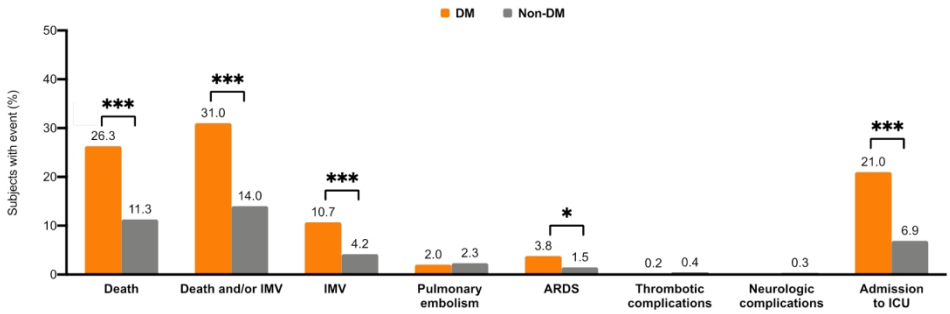

Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.

Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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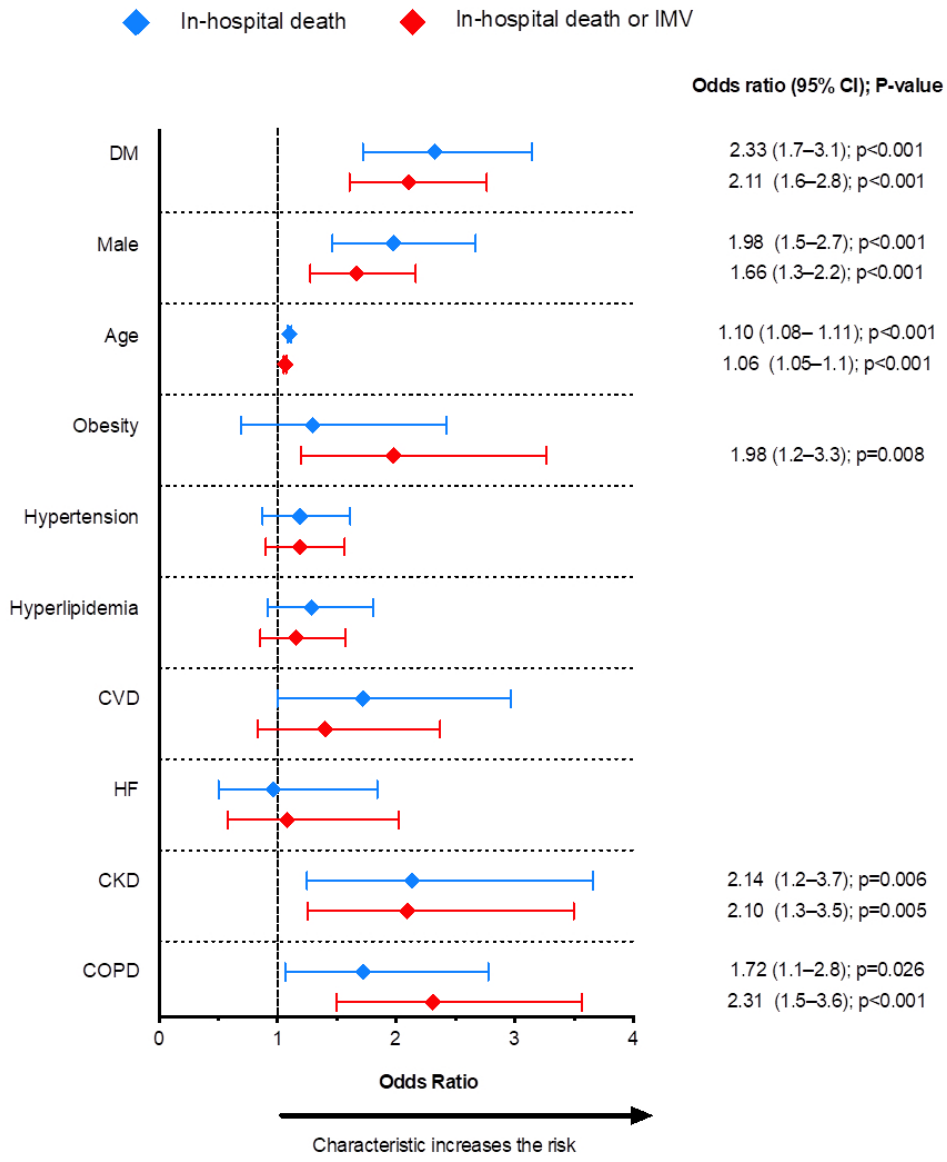

Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death or invasive mechanical ventilation.

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

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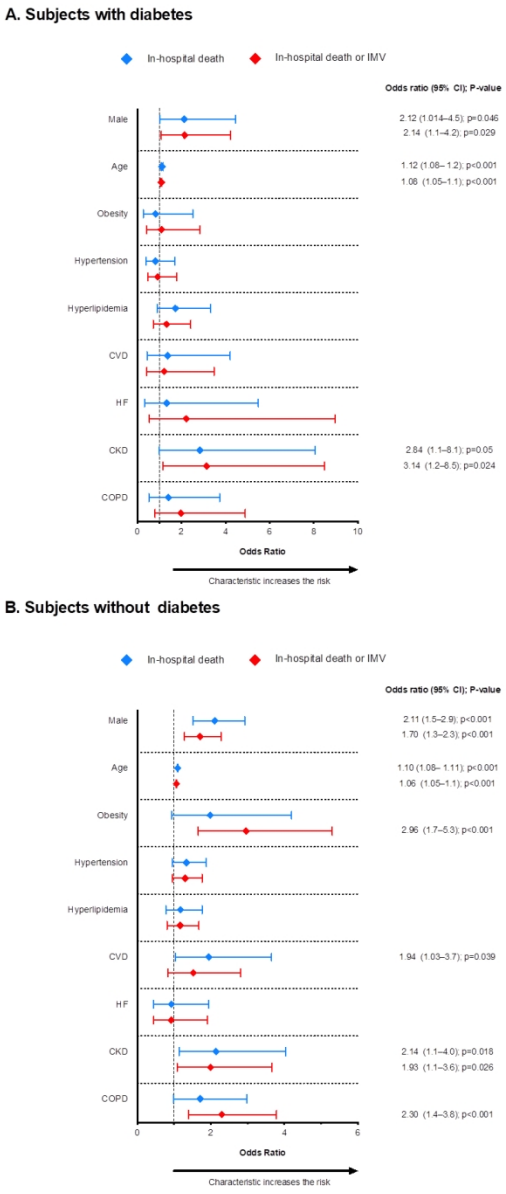

Figure 4. Clinical and demographic variables associated with increased risk of in-hospital death and the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes (A) and without diabetes (B).

Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical ventilation

218x505mm (96 x 96 DPI)

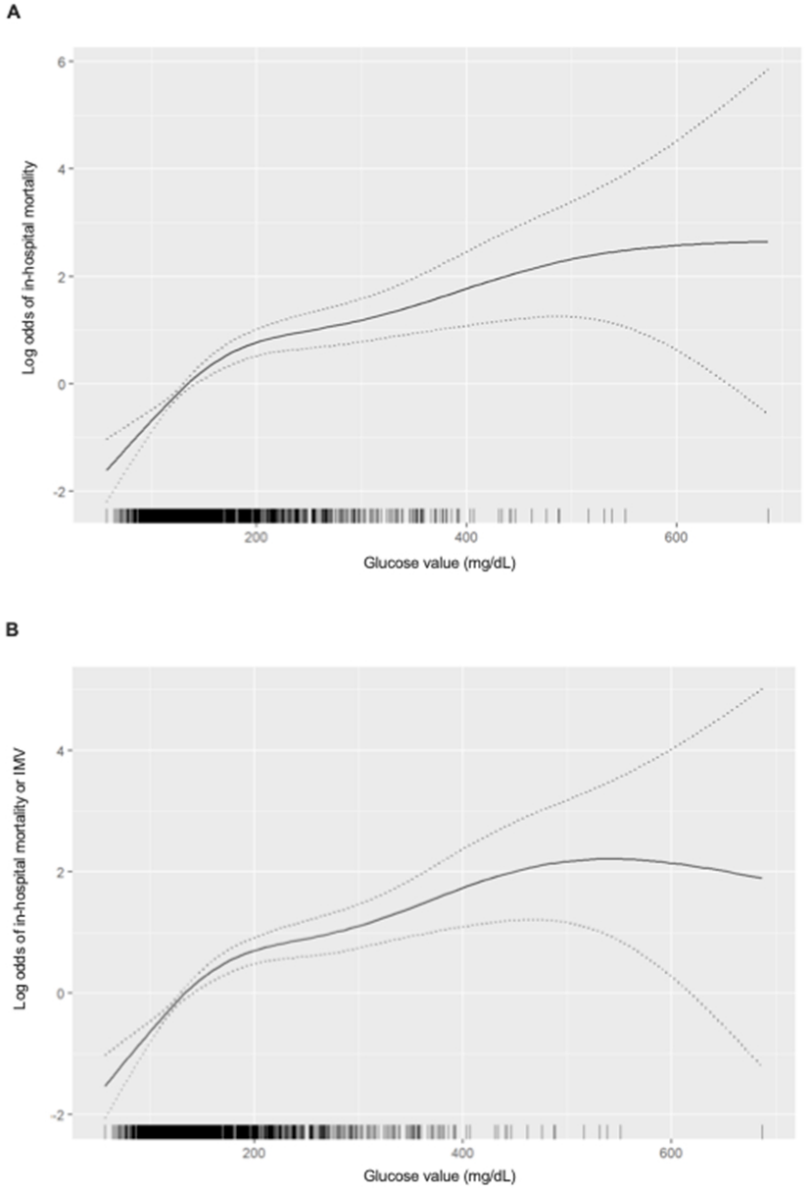

Figure 5. Spline plot demonstrating a marked non-linearity in the relationship between plasma glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive mechanical ventilation (IMV) rate (B). Tick marks above the horizontal axis indicate the values at which the observations were made. The dotted lines represent the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD.

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

219x323mm (96 x 96 DPI)

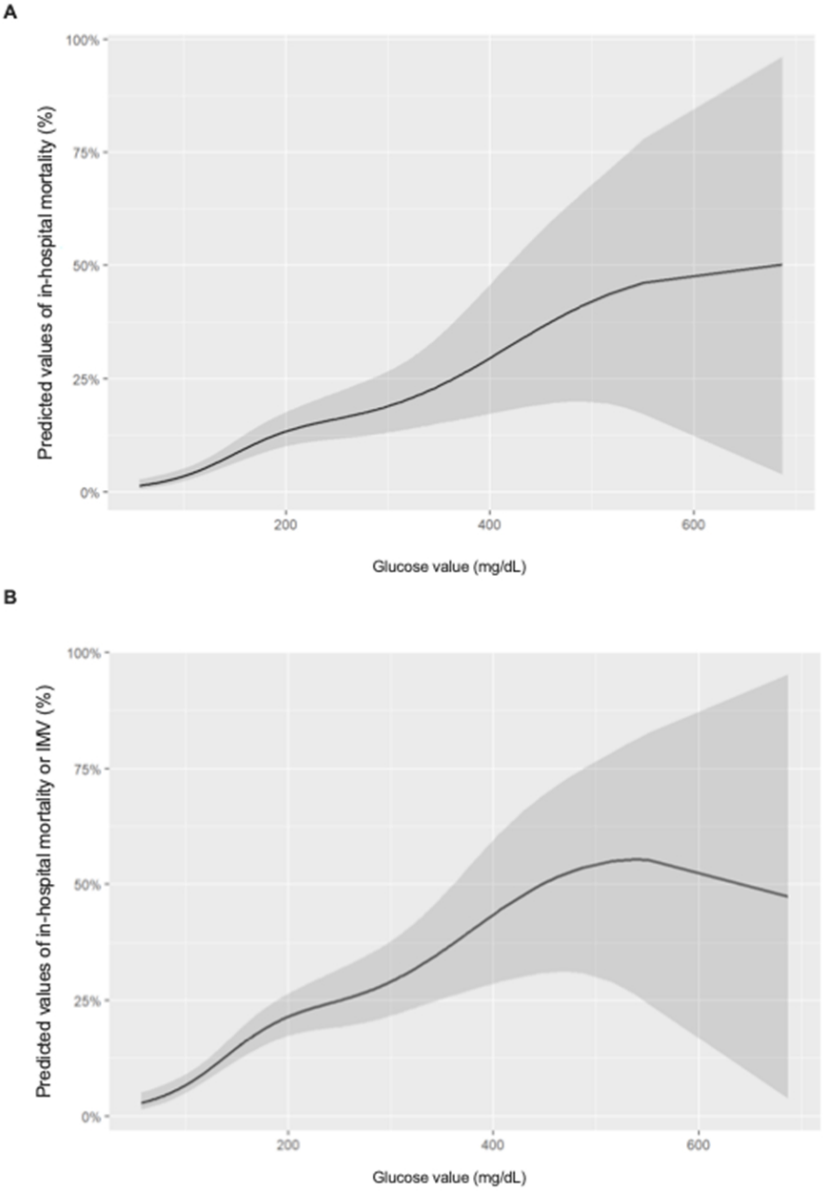

Figure 6. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized smoothing splines. The shaded area represents the 95% confidence interval. The model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD

Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

231x333mm (96 x 96 DPI)

ONLINE-ONLY SUPPLEMENTARY MATERIALS

These supplemental materials have been provided by the authors to give the readers additional information about the study.

Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

Emilio Ortega [1,2,3], Rosa Corcoy [4,5,6], Mònica Gratacòs[1], Xavier Cos-Claramunt [1,7], Manel Mata-Cases [1,8,10], Ramon Puig- Treserra[1], Jordi Real [1], Bogdan Vlacho [1], Esmeralda Castelblanco [1,8], Pere Domingo [9], Kamlesh Khunti [11], Josep Franch-Nadal [1,8,12]* and Dídac Mauricio [1,4,8,13]*

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Supplementary Table 1. Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus

	Diabetes N=448	**No diabetes N=1621**	p-value
Vital signs			
Systolic blood arterial pressure, mean (SD), mmHg	128 (19.7)	123 (19.3)	0.037
Diastolic blood arterial pressure, mean (SD), mmHg	72.0 (12.1)	71.1 (12.5)	0.501
Heart rate, mean (SD), bpm	80.2 (14.7)	79.4 (14.9)	0.641
Temperature, mean (SD), °C	36.5 (0.823)	36.5 (0.805)	0.086
Basal laboratory measurements			
Renal function			
Glomerular filtration (CKD-EPI), mean (SD), mL/min/1.73 m²	73.5 (26.5)	81.2 (23.9)	<0.001
Creatinine, mean (SD), mg/dL	1.09 (0.716)	0.943 (0.510)	<0.001
Inflammation markers			
Procalcitonin, mean (SD), ng/mL	0.661 (1.30)	0.387 (1.30)	<0.001
C-reactive protein, mean (SD), mg/L	97.1 (107)	75.9 (82.5)	<0.001
Other biochemical markers			
D-dimer, mean (SD), ng/mL	3990 (10800)	2340 (6720)	<0.001
Liver function			
Alkaline phosphatase, mean (SD), U/L	78.3 (39.1)	78.6 (62.3)	0.984
Lactate dehydrogenase, mean (SD), U/L	644 (399)	575 (311)	<0.001
Gamma-glutamyl transferase, mean (SD), U/L	93.8 (135)	88.4 (123)	0.804
Aspartate aminotransferase, mean (SD), U/L	49.6 (165)	42.7 (57.8)	0.022
Alanine aminotransferase, mean (SD), U/L	51.7 (136)	45.1 (60.6)	0.354
Haematology parameters			
Haemoglobin, mean, (SD), g/dL	13.1 (2.09)	13.6 (1.84)	0.433
Leucocytes, mean (SD), x10³/µL	8.91 (6.52)	7.47 (4.17)	<0.001
Platelets, mean (SD), x10³/µL	247 (112)	250 (116)	0.705

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Monocytes, mean (SD), %	7.21 (5.29)	8.19 (3.91)	<0.001
Lymphocytes, mean (SD), %	15.6 (10.0)	19.0 (10.9)	<0.001
Neutrophils, mean (SD), %	76.1 (13.5)	71.8 (13.5)	<0.001
Prothrombin time, mean (SD), s	15.6 (15.6)	14.8 (10.5)	0.076
Electrolytes			
Phosphorus, mean (SD), mg/dL	3.39 (0.971)	3.15 (0.731)	0.026
Sodium, mean (SD), mg/dL	138 (6.41)	138 (4.35)	0.537
Calcium, mean (SD), mg/dL	8.31 (0.648)	8.39 (0.574)	0.102
Blood gases			
CO_2 pressure, mean (SD), mmHg	37.8 (9.95)	35.8 (7.42)	0.007
O_2 pressure , mean (SD), mmHg	73.4 (35.4)	67.5 (30.9)	0.216
O_2 saturation, mean (SD), %	90.3 (11.4)	89.1 (13.6)	0.694

CKD-EPI, Glomerular filtration rate estimate based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

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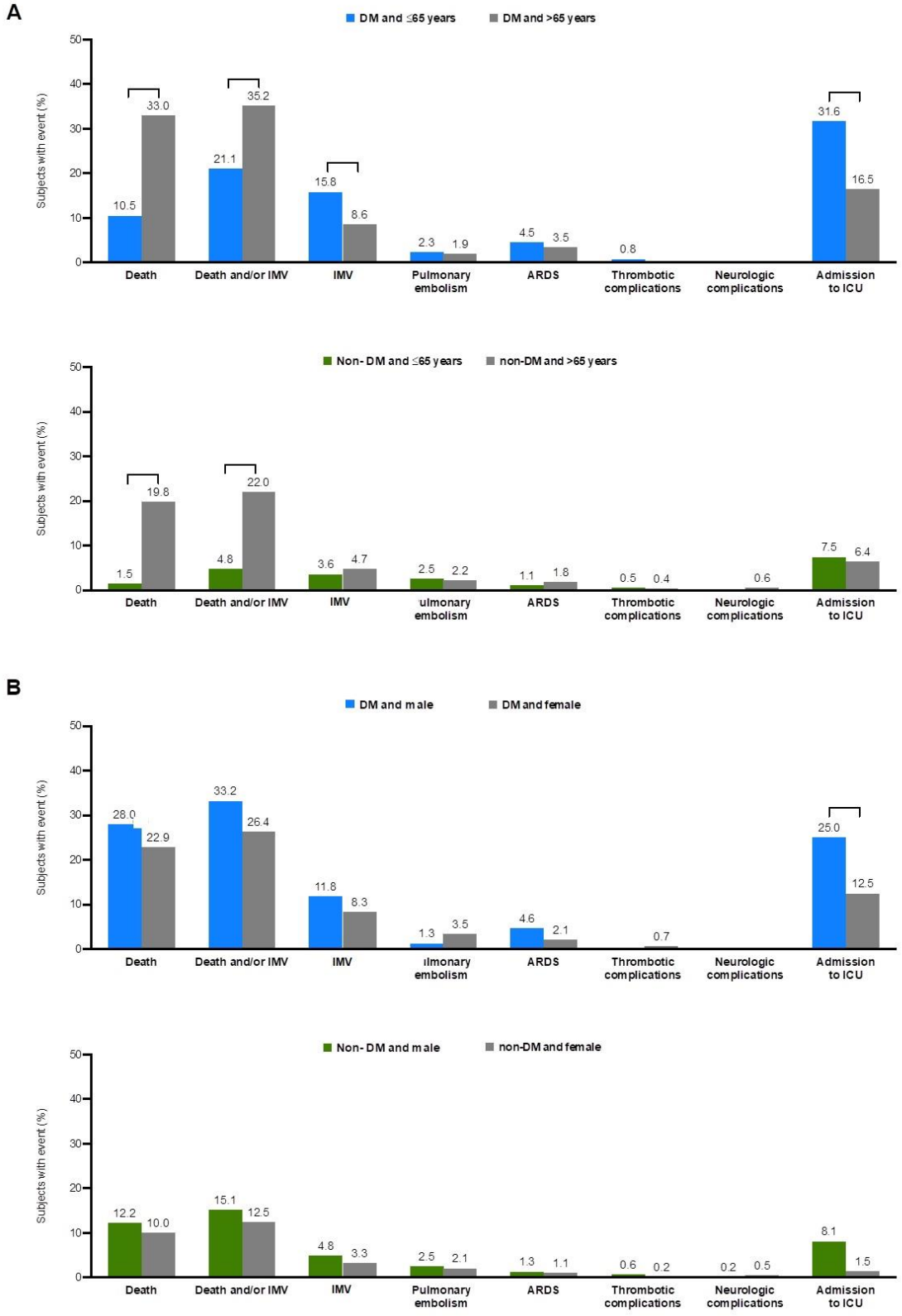
Supplementary Figure 1. Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).



ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05

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Supplementary table 2. Number of events in patients with pre-existing diabetes and stress hyperglycaemia/unknown diabetes

	Pre-existing diabetes (DM codes and/or HbA1c≥6.5% and/or antidiabetic treatment N=302	Stress hyperglycaemia/unknown diabetes glucose≥200 mg/dl or insulin use in the first 24 hours of admission N=146
Death	69 (22.8%)	49 (33.6%)
Death and or invasive mechanical ventilation	79 (26.2%)	60 (41.1%)
Invasive mechanical ventilation	22 (7.28%)	26 (17.8%)
Pulmonary embolism	5 (1.66%)	4 (2.74%)
Acute respiratory distress syndrome (ARDS)	7 (2.32%	10 (6.85%)
Thrombotic complications	1 (0.33%)	0 (0.00%)
Neurologic complications	0 (0.00%)	0 (0.00%)
Admission to intensive care unit	23 (7.62%)	71 (48.6%)

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Supplementary Table 3. Clinical characteristics at baseline as predictors of death vs death or invasive mechanical ventilation according to the model with all potential independent variables included

	Death			Death or invasive mechanical ventilation		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Diabetes (yes)	2.325 ***	1.719–3.144	<0.001	2.107 ***	1.608–2.761	<0.001
Sex (male)	1.977 ***	1.463–2.670	<0.001	1.663 ***	1.276–2.167	<0.001
Age (years)	1.102 ***	1.087–1.117	<0.001	1.063 ***	1.052–1.075	<0.001
Obesity (yes)	1.297	0.694–2.424	0.414	1.978 **	1.198–3.267	0.008
Hypertension (yes)	1.188	0.874–1.613	0.271	1.188	0.902–1.565	0.221
Hyperlipidaemia (yes)	1.289	0.919–1.808	0.141	1.158	0.853–1.572	0.346
Cardiovascular diseases (yes)	1.721	0.999–2.966	0.051	1.403	0.830–2.370	0.206
Heart failure (yes)	0.964	0.504–1.842	0.911	1.082	0.578–2.023	0.806
Chronic renal insufficiency (yes)	2.135 **	1.246–3.659	0.006	2.096 **	1.255–3.498	0.005
COPD (yes)	1.721 *	1.066–2.779	0.026	2.310 ***	1.498– .564	<0.001
Observations	2069			2069		
R2 Tjur	0.208			0.157		
Hosmer–Lemeshow test	0.26			0.94		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 4. Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.

	Death		
Predictors	Odds Ratios	95% CI	p-value
Diabetes * Obesity	0.720	0.214–2.425	0.596
Diabetes * Hyperlipidaemia	0.766	0.407–1.442	0.408
Diabetes * Heart failure	1.406	0.373–5.298	0.614
Diabetes * Chronic kidney disease	0.805	0.273–2.371	0.693
Diabetes * COPD	0.631	0.235–1.696	0.361

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Supplementary Table 5. Clinical characteristics at baseline associated with in-hospital death stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	2.107 ***	1.516–2.929	<0.001	2.125 *	1.014–4.451	0.046
Age	1.096 ***	1.081–1.112	<0.001	1.124 ***	1.081–1.170	<0.001
Obesity	1.984	0.938–4.198	0.073	0.826	0.272–2.511	0.736
Hypertension	1.333	0.947–1.876	0.099	0.823	0.400–1.697	0.598
Hyperlipidaemia	1.173	0.780–1.765	0.443	1.729	0.899–3.326	0.101
Cardiovascular diseases	1.943 *	1.033–3.654	0.039	1.368	0.445–4.208	0.584
Heart failure	0.926	0.442–1.944	0.840	1.330	0.323–5.484	0.693
Chronic kidney disease	2.143 *	1.137–4.038	0.018	2.839 *	1.000–8.060	0.050
COPD	1.712	0.984–2.979	0.057	1.404	0.529–3.729	0.495
Observations	1795			274		
R2 Tjur	0.178			0.240		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 6. Clinical characteristics at baseline associated to in-hospital death or mechanical ventilation stratified for diabetes status (model 3, namely the model with all demographic and clinical variables included).

	Without diabetes			Diabetes		
Predictors	Odds Ratios	95% CI	p-value	Odds Ratios	95% CI	p-value
Sex (male)	1.710 ***	1.282–2.280	<0.001	2.138 *	1.081–4.226	0.029
Age	1.061 ***	1.050–1.073	<0.001	1.082 ***	1.047–1.118	<0.001
Obesity	2.958 ***	1.651–5.298	<0.001	1.090	0.420–2.827	0.860
Hypertension	1.297	0.955–1.762	0.096	0.920	0.473–1.789	0.806
Hyperlipidaemia	1.165	0.811–1.675	0.408	1.326	0.728–2.415	0.356
Cardiovascular diseases	1.525	0.827–2.814	0.177	1.217	0.426–3.477	0.714
Heart failure	0.923	0.447–1.906	0.829	2.219	0.549–8.971	0.264
Chronic kidney disease	1.993 *	1.084–3.662	0.026	3.140 *	1.163–8.474	0.024
COPD	2.298 **	1.396–3.781	0.001	1.976	0.800–4.885	0.140
Observations	1795			274		
R2 Tjur	0.129			0.190		

p<0.05 ** p<0.01 *** p<0.001

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Supplementary Table 7. Multivariate model of the association between predictors and the odds of death and death or invasive mechanical ventilation based on the nonlinear glucose curve.

	Death			Death or Invasive mechanical ventilation		
Predictors	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Sex (male)	1.911 ***	1.375–2.655	<0.001	1.540 **	1.159–2.047	0.003
Age	1.108 ***	1.090–1.125	<0.001	1.062 ***	1.049–1.074	<0.001
Obesity	1.079	0.527–2.206	0.836	1.814 *	1.057–3.112	0.031
Hypertension	1.109	0.800–1.537	0.534	1.134	0.849–1.515	0.394
Hyperlipidaemia	1.330	0.928–1.906	0.120	1.152	0.837–1.585	0.386
Cardiovascular diseases	1.686	0.958–2.967	0.070	1.356	0.792–2.325	0.267
Heart failure	0.768	0.388–1.520	0.448	0.911	0.472–1.757	0.781
Chronic kidney disease	2.251 **	1.268–3.996	0.006	2.151 **	1.250–3.701	0.006
COPD	1.666 *	1.006–2.760	0.047	2.253 ***	1.436–3.536	<0.001
Observations			1877			1877
R2			0.241			0.188

p<0.05 ** p<0.01 *** p<0.001

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Covid Data Save Lives

HM Hospitales makes an anonymous dataset freely available to the international medical and scientific community with all the available clinical information on patients treated in our hospital centers for the SARS-CoV-2 virus

Compared to most of the existing **databases on COVID-19,** focused on demographic data, this clinical dataset collects the different interactions in the **COVID-19 treatment process, including detailed information on diagnoses, treatments, admissions, ICU admissions, diagnostic imaging tests, laboratory results, discharge or death, among many other records.**
With the opening of this dataset, we intend to take the first step and serve as an example for other institutions to be encouraged to share their information and thus, together, be able to offer the medical and scientific community clinical data with which to obtain predictive models of evolution, epidemiological models, information on the response to the various treatments applied, **knowledge of virus for the creation of a vaccine, and sociodemographic data on the impact on the population of the virus.**

Dataset “Covid Data Save lives”

The information in this data set comes from the HM Hospitales EHR system. It contains the anonymized records of 2,310 patients, admitted with a diagnosis of COVID POSITIVE or COVID PENDING, since the beginning of the epidemic to date. The information is organized in tables according to their content, all of them linked by a unique admission identifier. This identifier is the de-anonymization key, explicitly created for this purpose, and has nothing to do with the actual identifier of each admission.

- The main table includes data on the admission and the patient (age and sex), data on the previous emergency if there has been one (2,226 records), data on their stay in the ICU if there has been one and records of the first and last set of emergency constants.
- The medication table shows all the medication administered to each patient during admission (more than 60,000 records), with the dates

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corresponding to the first and last administration of each drug, identified by their brand name and classification in the ATC5/ATC7.

- In the table of vital signs, there are all the basic records of constants (54,000 records so far) collected during admission with their date and time of registration.
- The laboratory table contains the results of the determinations (398,884 records) of all the requests made to each patient during admission and in the previous emergency, if any.
- And finally, the ICD10 coding tables show the records of diagnostic and procedural information coded according to the international ICD10 classification in its latest distributed version (does not include COVID), for the patients referred, both for episodes of hospital admission (more than 1,600) and for the emergency (more than 1,900) prior to those episodes, if any.

Web page: https://www.hmhospitales.com/coronavirus/covid-data-save-lives/english-version

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

Risk factors for severe outcomes in people with diabetes hospitalized for COVID-19: A cross-sectional "Covid Data Save Lives" database study

Emilio Ortega, Rosa Corcoy,Mònica Gratacòs, Xavier Cos-Claramunt , Manel Mata-Cases , Ramon Puig- Treserra, Jordi Real , Bogdan Vlacho , Esmeralda Castelblanco , Pere Domingo , Kamlesh Khunti , Josep Franch-Nadal and Dídac Mauricio

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	**Abstract**
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			**Page 4-5 Lines: 2-24 and 1-22**
Objectives	3	State specific objectives, including any prespecified hypotheses			**Page 6 Lines: 4**
Methods					

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Study Design	4	Present key elements of study design early in the paper			**Page 7 Lines: 3-4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			**Page 7 Lines:4-11**
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	**Page 7 Lines:19-24 Page 8 Lines:1-4**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	**Page 8 Lines:5-14**

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Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			**Page 7 Lines:12-16**
Bias	9	Describe any efforts to address potential sources of bias			**Page 9 Lines:1-7**
Study size	10	Explain how the study size was arrived at			**NA**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			**Page 8 Lines:21-24**
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity			**Page 8 Lines:21-24 Page 9 Lines: 1-12**

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		analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	**Page 7 Lines:12-18**
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	**NA**
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	**Page 9 Lines:18-24**
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data			**Page 10 Lines:1-11**

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		for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			**Page 10** **Lines: 12-19**
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			**Page 10** **Lines:20-25** **Page 11** **Lines: 1-23** **Page 12** **Lines:1-4**
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			**Page 12** **Lines5-17**
Discussion					
Key results	18	Summarise key results with reference to study objectives			**Page 12** **Lines: 19-24**
Limitations	19	Discuss limitations of the study,		RECORD 19.1: Discuss the	**Page 14**

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		taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	**Lines:22-24 Page 15 Lines:1-22**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			**Page 13 Lines:1-22 Page 14 Lines: 1-20**
Generalisability	21	Discuss the generalisability (external validity) of the study results			**Page 16 Lines:1-10**
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			**Page 17 Lines: 11**
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	**Page 17 Lines:12-13**

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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