

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-051237
Article Type:	Original research
Date Submitted by the Author:	15-Mar-2021
Complete List of Authors:	Ortega, Emilio; Hospital Clinic de Barcelona Corcoy, Rosa; Hospital de la Santa Creu i Sant Pau, Gratacòs , Mònica; IDIAP Jordi Gol Cos Claramunt, Francesc Xavier; IDIAP Jordi Gol Mata-Cases, Manel; IDIAP Jordi Gol, DAP-Cat Group, Unitat de Suport a la Recerca Barcelona; Institut Catala De La Salut, La Mina Primary Health Care Centre Puig- Treserra, Ramon ; IDIAP Jordi Gol Real, Jordi; Institut Universitari d'Investigaci Primaria Jordi Gol (IDIAP Jordi Gol), DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat Vlacho, Bogdan; IDIAP Jordi Gol Castelblanco, Esmeralda; Hospital de la Santa Creu i Sant Pau, Endocrinology Domingo, Pere; Hospital de la Santa Creu i Sant Pau, Infectious Diseases Khunti, Kamlesh; University of Leicester, Diabetes Research Centre Franch-Nadal, Josep; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut Mauricio, Didac ; Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Didac Mauricio
Keywords:	COVID-19, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < INFECTIOUS DISEASES
	1

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

reliez oni

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

Emilio Ortega ^{1,2,3}, Rosa Corcoy ^{4,5,6}, Mònica Gratacòs¹, Xavier Cos-Claramunt ^{1,7}, Manel Mata-Cases ^{1,8,10}, Ramon Puig- Treserra¹, 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*}

11	6	
12 13	7	¹ DAP-Cat group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la recerca a
14	8	l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain;
15	9	² CIBER of physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III
16 17	10	(ISCIII), Spain
18	11	³ Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi i Suñer,
19	12	Hospital Clinic, Barcelona, Spain;
20 21	13	⁴ Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau;
22	14	⁵ Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
23 24 25	15 16	⁶ CIBER of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Instituto de Salud Carlos III (ISCIII), Spain
26	17	⁷ Innovation office at Institut Català de la Salut, Barcelona, Spain
27 28 29	18 19	⁸ CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Spain
30 31	20 21	⁹ Infectious Diseases, Hospital Universitari de la Santa Creu i Sant Pau, Institut de Recerca Hospital Universitari de la Santa Creu i Sant Pau;
32 33 34	22 23	¹⁰ Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Sant Adrià de Besòs, Spain
35	24	¹¹ Diabetes Research Centre, University of Leicester, Leicester, UK;
36 37 38	25 26	¹² Primary Health Care Center Raval Sud, Gerència d'Atenció Primaria, Institut Català de la Salut, Barcelona Spain
39	27	¹³ Departament of Medicine, University of Vic - Central University of Catalonia, Vic, Barcelona, Spain.
40 41	28	
42	29	
43	30	
44 45	31	
45 46	32	
47	33	
48	34	
49 50	35	
51	36	
52	37	
53 54	38	
55	30	
56	40	
57 58	т и //1	
59	41 40	
60	42	

1		
2		
5 4	1	
5	2	*Corresponding authors
6	3	Dr Dídac Mauricio
/ 8	4	Hospital de la Santa Creu i Sant Pau
9	5	Sant Quintí, 89
10	6	08041 Barcelona, Spain
11	7	Telephone No.: +34 935565661; Fax No.: +34 9355602
13	8	Email: <u>didacmauricio@gmail.com</u>
14	9	
15 16	10	Dr Josep Franch-Nadal
17	11	Centre d'Atenció Primària Raval Sud,
18 10	12	Av. Drassanes, 17-21,
20	13	08001 Barcelona, Spain
21	14	Telephone No.: +34 933294495; Fax No.: +34 9344277 63
22 23	15	Email: josep.franch@gmail.com
24	16	
25	17	
26 27	18	Word count: abstract 301; main text 3734
28	19	Tables: 1
29	20	Figures: 2
30 31	21	References: 56
32	22	Appendix: Tables 6; Figures 11;
33		
34 35		
36		
37		
38 39		
40		
41 42		
42 43		
44		
45 46		
40 47		
48		
49 50		
50 51		
52		
53		
55		
56		
57		
58 59		
60		

1 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

5 Settings: We used pseudonymised medical records data provided by six general hospitals from the
6 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 21 COVID-19 infection, particularly among males, the elderly, and those with impaired kidney 22 function. Moreover, hyperglycaemia on admission is a strong predictor of poor outcomes,

1 ว		
2 3 4	1	suggesting that its optimisation in a personalised manner could help to improve the outcomes
5 6 7	2	during the hospital stay.
7 8 9	3	Keywords: COVID-19, Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation
10 11	4	
12 13 14	5	Strengths and limitations of this study
15		
16 17 18	6	• A major strength of our study is the thorough methodological approach to analyse the risk
19 20	7	of in-hospital COVID-19-related complications based on the presence of DM or overt
21 22 23	8	hyperglycaemia.
24 25	9	• We were limited by not having access to the patient's medical history prior to admission
26 27 28	10	and few registers for some important variables for diabetes (such as Hb1Ac) and no data on
20 29 30	11	weight or BMI (only the presence of obesity).
31 32 33	12	• The selection of subjects with DM was made based on a proxy algorithm (including DM
34 35	13	diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose
36 37 38	14	levels at admission.
39 40 41	15	• We used random blood glucose on admission for the spline analyses, thus preventing the
42 43	16	distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.
44 45 46	17	
47		
48 49		
50		
51 52		
53		
54 55		
56		
57 58		
59		
60		

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-19related 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

BMJ Open

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. beet teries only

1 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/m²], CVD, heart failure, cerebrovascular diseases, ischemic heart disease, chronic renal disease, chronic obstructive

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

3		
4		
5		
6		
7		
8		
9		
1	0	
1	1	
1	2	
1	3	
1	4	
1	5	
1	6	
1	7	
1	8	
1	9	
2	0	
2	1	
2	2	
2	3	
2	4	
2	5	
2	6	
2	7	
2	8	
2	9	
3	0	
3	1	
3	2	
3	3	
3	4	
3	5	
3	6	
3	7	
3	8	
3	9	
4	0	
4	1	
4	2	
4	3	
4	4	
4	5	
4	6	
4	7	
4	8	
4	9	
5	0	
5	1	
5	2	
5	3	
5	4	
5	5	
5	6	
5	7	
5	8	
5	9	

60

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.

11 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 %).

16 The association between the study outcomes (i.e., mortality and mortality or mechanical 17 ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and 18 associated risk factors. Several models of interest were tested, namely with the sequential inclusion 19 of different covariates and the estimated differences expressed as odds ratio (OR) and their 20 respective 95% confidence intervals (CI). To analyse the nonlinear relationship of random blood 21 glucose levels on admission with the two study outcomes, we used an adjusted semi-parametric 22 model (generalized additive model [GAM]) calculating the spline curves with two degrees of 23 freedom (knots) using the mgcv package in R, version 1.8-31[19] with adjustment for potential

1 confounders. Data management and statistical analyses were performed using the R statistical

2 software version 3.6.1 (<u>https://www.r-project.org/</u>).

3 2.5 Patient and Public Involvement

4 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination5 plans of our research.

- 6 3. Results
- 7 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 m² vs. 81.2±23.9 mL/min/1.73 m²; 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

22 (3990 ±10800 ng/mL vs .2340 ±6720 ng/mL, respectively).

23 3.2 Events and complications during in-hospital stay

BMJ Open

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

emerged as an independent predictor (OR=1.98, 95% CI=1.5–2.7) (Figure 2, Supplementary Table

(i.e., age, sex, diabetes, CKD, and COPD) were identified as increasing the risk. In additon, obesity

2).

The multiple logistic regression models were repeated to rule out the potential interaction of DM

2 3	1
4 5	1
6 7	2
8 9	3
) 10 11	4
12 13 14 15	5
16 17	6
18 19	7
20 21 22	8
22 23 24	9
25 26	10
27 28	11
29 30	12
31 32 33 34 35	13
36 37	14
38 39	15
40 41 42	16
43 44	17
45 46	18
47 48	19
49 50	20
51 52	21
53 54	22
55 56 57	23
58 59 60	_5

1

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2 with different clinical conditions (i.e., obesity, hyperlipidemia, obesity and hyperlipidemia, HF, 3 CKD, and COPD) for the in-hospital death outcome. The results showed none of these conditions 4 affected the relationship between the risk of death and DM (Supplementary Table 3). 5 3.4. Factors predicting hospital death and death or IMV by comorbid diabetes 6 A sub-analysis was done separately for subjects with or without DM. In the DM subgroup, the only 7 variables independently predicting the risk of both mortality and death or IVM were male sex, 8 older age, and CKD (Figure 3A and Supplementary Table 4 and 5). In contrast, in subjects without 9 DM, besides the above variables, the odds of death were also increased among subjects with CVD 0 (OR=1.94, 95% CI=1.03–3.7), and the odds of death or IVM among those with obesity or COPD 1 (OR=2.96, 95% CI=1.7-5.3 and OR=2.30, 95% CI= 1.4 - 3.8, respectively) (Figure 3B and 2 Supplementary Table 4 and 5). 3.5. Factors predicting hospital death and death or IMV by glucose levels at admission 3 4 We used non-parametric logistic regression models to assess whether there was a relationship 5 between random BG on admission and the risk of mortality (and death or IMV). We observed a 6 marked non-linearity in the effect of BG on admission in the risk of both outcomes (Figure 4A and 7 **4B** and **Supplementary Table 6**). While the risk was increased among subjects with high random 8 BG levels on admission, the magnitudes of the predicted mortality differed depending on the 9 baseline values, with a large increase in the log-odds of death or IVM with values up to 200 mg/dL 20 (11.1 mmol/L) and smaller increases above this level. The prediction models (Figure 5A and 5B) 21 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

23 that beside glucose at admission male sex, older age, CKD, and COPD were predictive of in-

BMJ Open

3		
4		
5		
6		
7		
, Q		
0		
ש 1	^	
1	1	
1	1	
1	2	
1	3	
1	4	
1	5	
1	6	
1	7	
1	8	
1	9	
2	0	
2	1	
2	2	
2	- २	
2 ว	ر ۸	
2 7	4 5	
2 7	с С	
2	0	
2	/	
2	8	
2	9	
3	0	
3	1	
3	2	
3	3	
3	4	
3	5	
3	6	
3	7	
3	8	
3	9	
4	0	
4	1	
4	2	
4	3	
4	4	
4	5	
4	6	
4	7	
4	8	
4	9	
5	0	
5	1	
5	2	
5	- २	
5	⊿	
5	-T 5	
5	6	
5	7	
5	γ Q	
5	0 0	
د	9	

60

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

3 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.

10 Diabetes is more frequent among subjects with COVID-19 needing hospital admission than those 11 that do not, with prevalence ranging between 8% and 37% depending on the region [12]. Indeed, 12 while the prevalence of DM in Spain has been estimated to be 13.8% of the general population, DM 13 was present in 21.7% of the hospitalised subjects in our study. This figure is in line with the 18.9% 14 prevalence reported in a retrospective cohort registry involving 109 hospitals in Spain [20]. It also 15 concurs with the 16.7% recently published for the first COVID-19 wave by the working group for 16 the surveillance and control of COVID-19 in Spain [21]. It is as well within the DM prevalence range 17 reported by a meta-analysis of international studies (mean 13.4%, ranging between 7.2% and 21.3%) 18 [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

2
3
4
5
6
7
8
9
10
11
12
12
13
14
15
16
17
18
19
20
21
22
22 22
∠_) ⊃4
24
25
26
27
28
29
30
31
32
22
27
34
35
36
37
38
39
40
41
42
43
11
44
45
46
47
48
49
50
51
52
53
57
54
55 57
56
57
58
59
60

1

1	by one French and two Chinese studies (20.4%, 10.6%, and 8.0%-14.5%, respectively) [26-28]. In
2	contrast, our rate was lower than this outcome in a population-based study from the UK in 23,804
3	COVID-19 patients with DM, where in-hospital deaths occurred in 31.4% of T2DM individuals [29].
4	Differences between studies and centres could be attributed to different treatment guidelines,
5	manners of identifying individuals with diabetes, and different proportions of DM patients with
6	severe vs. non-severe disease. Indeed, COVID-19 patients with DM are more severely ill at initial
7	presentation and, when in hospital, they have a 2-fold higher risk of severe infection than those
8	without DM [15]. In turn, the death rate in DM patients with a severe illness can be up to 3-fold
9	higher than this of patients with a non-severe course [12, 15, 22]. Different meta-analyses have
10	reported that higher mean age and male sex among infected with SARS-CoV-2 are associated with a
11	more severe infection and higher fatality than those with the non-severe disease [11, 27, 30]. In the
12	same line, studies assessing the phenotypic characteristics of COVID-19 patients with pre-existing
13	DM have found that those with severe infection were older, had more comorbidities (i.e.,
14	cerebrovascular disease, CVD, hypertension, and COPD), and increased values of inflammation
15	and endothelial and coagulation dysfunction markers (e.g., D-dimer, procalcitonin, and
16	thrombocytopenia) than those without DM [26-28,31,32]. Our study confirms these findings, as the
17	proportion of severe SARS-CoV-2 cases (e.g., requiring IVM or ICU admission) in the DM
18	population was higher. They were more frequently male and over 65 years, had more comorbid
19	conditions, and higher levels of inflammatory and endothelial and coagulation dysfunction markers
20	than non-DM patients on admission.
0.1	
21	Different meta-analyses have identified CKD as a risk factor for severity and in-hospital death in
22	SARS-CoV-2 patients [7, 25, 22, 33]. Moreover, a recent study conducted in Danish hospital-
23	diagnosed COVID-19 patients reported that kidney insufficiency was independently associated
24	with progressive risk of severe disease or death [34]. Although it is difficult to distinguish whether

- 25 poor outcomes are linked to acute kidney injury (AKI) developed during the course of the disease
 - For peer review only http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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)

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.

8 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2	
3	
4	
5	
6 7	
/	
8	
9	
10	
11	
12	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
4Z	
45 11	
44 45	
45 46	
40	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

60

1 received potentially life-saving ICU care. This might be reflected in our results, where in-hospital

2 death was more frequent among those over 65 years, but ICU admission was more frequent among

3 those ≤ 65 years.

For beet teries only

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.

1		
2		
3	1	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,
4	2	R.C,M.M-C, B.V, K.K,D.M.; formal analysis, R.P-T.; resources and data curation, R.P-T and B.V.; writing-
5	3	original draft preparation, B.V and M.G.; writing-review and editing, E.O.J.F-N, R.C.M.M-C.M.G, X.C-C, E.C.
6	4	B.V, K.K,D.M and P.D.; supervision: D.M, R.C and J.F-N.; project administration: B.V.
/	5	A 1 and 1 descent COMP DATA CANELINES Have 'the UNA (second 'd'an detailed CIPED (D'date
8	5	Acknowledgements: COVID DATA SAVE LIVES -Hospitales HM for providing database. CIBER of Diabetes
9	07	and Associated Metabolic Diseases (CIBERDEM) and CIBER of physiopathology of obesity and Nutrition
10	8	(CIDEROBN) are initiatives from Instituto de Salud Carlos III, Madrid, Spain. The authors acknowledge Amanda Brower (Lagheida Madigal communications Ltd.) for providing support in the paper aditing. KK is supported
10	0	by the National Institute for Health Research (NIHP) Applied Research Collaboration East Midlands (APC EM)
12	10	and the NIHR L eigester Biomedical Research Centre (BPC)
14	10	and the Wirth Eclesici Dionedical Research Centre (DRC).
15	11	Funding: This study was supported by Primary Care Diabetes Europe grant (grant number FEr20/0020)
16	12	Data sharing: The data controller for Hospitales HM does not allow the sharing of raw data. Statistical codes are
17	13	available upon request from the corresponding authors (I.FN or D.M).
18	1 /	
19	14	Conflicts of interest: The funders had no role in the design of the study; in the collection, analyses, or
20	15	interpretation of data; in the writing of the manuscript, or in the decision to publish the results.
21	16	E.O. has received advisory and or speaking fees from Astra-Zeneca, Boehringer Ingelheim, Lilly, MSD, Novo
22	17	Nordisk, Sanofi, and Amgen; he has received research grants to the institution from MSD and Amgen.
23	18	R.C. has received advisory and/or speaking fees from Abbott. Ascensia, Lilly, MSD, Novo Nordisk and Sanofi
24	10	
25	19	M. M-C. has received advisory honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD,
20	20	Novartis, Novo Nordisk, and Sanofi; he has received speaker honorarium from Astra-Zeneca, Bayer, Boehringer
27	$\frac{21}{22}$	Ingelheim, GSK, Lilly, Menarini, MSD, Novartis, Novo Nordisk, and Sanoti; he has received research grants to
20		the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanon.
30	23	J. F-N has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK,
31	24	Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-
32	25	Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.
33	26	KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca.
34	27	Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Baver, Berlin-
35	28	Chemie AG / Menarini Group, Janssen, and Napp
36	20	
37	29	D. M. has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK,
38	30 21	Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-
39	51	Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.
40	32	P. D. has received lecture and Advisory Board fees from Gilead Siciences, Roche, Merck, Sharp & Dohme, ViiV
41	33	Healthcare, Janssen & Cilag, Theratechnologies, Boehringer Ingelheim, and Ferrer International. PD has received
42	34	research grants from Gilead Siciences, ViiV Healthcare, GSK, Janssen & Cilag, and Boehringer Ingelheim.
43	35	B V X C-C LR R P-T M G and E C have no conflict of interest to declare
44 45		
45 46	36	
47	•••	
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		

1 References

1 2 3

4 5

6 7

8

9

10 11 12

13

14

15

23

29

30

2 **1.** World Health Organization. 15-Novel Coronavirus(2019-nCoV). WHO Bull 2020; 1–7.

3 2. Agència de Salut Pública de Catalunya (ASPCAT). Informe tècnic resum dels casos de covid-19
a Catalunya, http://salutpublica.gencat.cat/web/.content/minisite/aspcat/butlletins/vigilanciaaspcat/2

5 020/45/INFORME-TECNIC-3-COVID-19_020420.pdf (2020).

6 3. Linde, Pablo (1 de febrero de 2020). «Sanidad confirma en La Gomera el primer caso de
7 coronavirus en España». El País. ISSN 1134-6582. Consultado el 10 de marzo de 2020. Available

- 8 from: https://elpais.com/sociedad/2020/01/31/actualidad/1580509404_469734.htm
- 9
 4. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. American
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
 10
- 19 20 11 5. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associat
- 11
 20
 11
 5. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated
 21
 12
 with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis 2020; 99: 47–
- 22 13 56.
- 14 6. Deng G, Yin M, Chen X, et al. Clinical determinants for fatality of 44,672 patients with COVID-19.
 15 Crit Care 2020; 24: 179.
- 27 16
 28 7. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, et al. Predictors of in-hospital COVID-19
 28 17 7. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, et al. Predictors of in-hospital COVID-19
 - mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex
 and health conditions. PLoS One 2020; 15: e0241742.
- 8. Papazafiropoulou AK, Antonopoulos S. The COVID-19 pandemic and diabetes mellitus.
 20 Archives of Medical Sciences. Atherosclerotic Diseases 2020;5:e200.
- 9 McDonald HI, Nitsch D, Millett E, Sinclair A, Thomas SL. New estimates of the burden of acute community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using linked electronic health records. Diabetic Med 2014;31(5):606-614.
- 24 10. Li S, Wang J, Zhang B, Li X, Liu Y. Diabetes mellitus and cause-specific mortality: a population 25 based study. Diabetes & metabolism journal 2019;43(3):319-341.
- 42
 43
 44
 45
 26
 11. Del Sole F, Farcomeni A, Loffredo L, Carnevale R, Menichelli D, Vicario T, et al. Features of severe COVID-19: A systematic review and meta-analysis. Eur J Clin Invest 2020;50:0–1.
 45
 46
 47
 47
 48
 49
 49
 49
 40
 40
 40
 41
 42
 44
 45
 46
 47
 47
 48
 49
 49
 49
 40
 40
 41
 42
 43
 44
 45
 44
 45
 46
 47
 47
 47
 48
 49
 49
 49
 40
 40
 40
 40
 41
 42
 44
 45
 45
 46
 47
 47
 48
 49
 49
 49
 40
 40
 40
 40
 40
 41
 41
 42
 43
 44
 44
 45
 45
 46
 47
 47
 48
 49
 49
 40
 40
 40
 40
 40
 41
 41
 42
 43
 44
 44
 45
 44
 45
 45
 46
 47
 47
 47
 48
 49
 49
 49
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 41
 41
 42
 44
 44
 45
 46
 47
 47
 47
 48
 49
 49
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
 40
- 46
 47 29 12. Pugliese G, Vitale M, Resi V, Orsi E. Is diabetes mellitus a risk factor for COronaVIrus Disease
 48 30 19 (COVID-19)? Acta Diabetol 2020;19. <u>https://doi.org/10.1007/s00592-020-01586-6</u>.
- 50 31 13. Peric S, Stulnig TM. Diabetes and COVID-19. Wien Klin Wochenschr 2020;132:356–61.
 51 32 doi:10.1007/s00508-020-01672-3
- 33
 33
 34
 34
 35
 35
 36
 37
 38
 39
 39
 30
 30
 31
 31
 32
 33
 34
 35
 35
 35
 36
 36
 37
 38
 39
 39
 30
 31
 31
 32
 32
 33
 33
 33
 33
 34
 35
 35
 36
 36
 37
 38
 39
 39
 30
 31
 32
 33
 33
 33
 34
 35
 35
 36
 36
 37
 38
 39
 39
 39
 30
 30
 31
 32
 32
 33
 33
 34
 35
 35
 36
 37
 37
 38
 39
 39
 30
 30
 31
 31
 32
 32
 33
 34
 35
 35
 36
 37
 37
 38
 39
 39
 30
 30
 31
 32
 32
 33
 34
 34
 35
 35
 36
 37
 37
 38
 39
 39
 30
 30
 31
 31
 32
 32
 34
 34
 35
 35
 36
 37
 37
 38
 38
 39
 39
 30
 30
 30
 31
 32
 32
 33
 34
 34
 35
 36
 37
 37
 38
 38
 39
 39
 30
 30
 31
 31
 32
 32
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 35
 36
 36
 36
 36
 36
 <

57 58 36 59 37 59 37 59 37 59 37 59 37 59 37 59 37 59 37 59 37 59 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 50 37 <li

1		
2	1	
4	1	16. Mantovani A, Byrne CD, Zheng M, Targher G. Diabetes as a risk factor for greater COVID-19
5	2	severity and in-hospital death: A meta-analysis of observational studies. Nutrition, Metabolism and
6	3	Cardiovascular Diseases 2020;30(8):1236-1248.
7	Δ	17 Soriguer F. Coday A. Bosch Comas A. Bordiý F. Callo Pasqual A. Carmona R. et al. Provalence
8	+ 5	of diabatas mollitus and impaired glucosa regulation in Spain: the Di@batas Study. Diabatalogia
9 10	6	2012: 55(1):88-93
11	0	2012, 00(1).00 90.
12	7	18. Caballero AE, Ceriello A, Misra A, et al. COVID-19 in people living with diabetes: An
13	8	international consensus. J Diabetes Complications 2020; 34: 107671.
14		
15	9	19. Wood S (2019) mgcv: mixed GAM computation vehicle with automatic smoothness estimation.
10	10	R-package version 1.8–31. https://CRAN.R-project.org/package=mgcv
18		
19	11	20. Carrasco-Sánchez FJ, López-Carmona MD, Martínez-Marcos FJ, et al. Admission
20	12	hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of
21	13	diabetes status: data from the Spanish SEMI-COVID-19 Registry. Ann Med 2021; 53: 103–116.
22	1.4	
23	14	21. Borobia A, Carcas A, Arnalich F, et al. A Cohort of Patients with COVID-19 in a Major Teaching
24 25	15	Hospital in Europe. J Clin Med 2020; 9: 1733.
26	16	22 Casin W group for the surrectillar of C 10 in Casin W group for the surrectillar of
27	10	22. Spain w group for the surveinance and control of C-19 in, Spain w group for the surveinance
28	17	and control of C-19 III, Redondo-Bravo L, et al. The first wave of the COVID-19 pandemic in Spain:
29	10	2020.25.2001421 doi:10.2807/1560.7017 ES.2020.25.50.2001421
30	19	2020,23.2001451. d01.10.2807/1500-7917.E3.2020.25.50.2001451
31	20	23. Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with
33	21	mortality in patients with <scp>COVID</scp> -19: A systematic review and meta-analysis. Diabetes.
34	22	Obes Metab 2020;22:1915–24. doi:10.1111/dom.14124
35		
36	23	24. Rivera-Izquierdo M, del Carmen Valero-Ubierna M, R-delAmo JL, et al. Sociodemographic,
37	24	clinical and laboratory factors on admission associated with COVID-19 mortality in hospitalized
38	25	patients: A retrospective observational study. PLoS One 2020; 15: e0235107.
39 40		
41	26	25. Laguna-Goya R, Utrero-Rico A, Talayero P, et al. IL-6–based mortality risk model for
42	27	hospitalized patients with COVID-19. J Allergy Clin Immunol 2020; 146: 799-807.e9.
43	20	
44	28	26. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic
45	29	characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study.
46 47	30	Diabetologia 2020;63:1500–15. <u>https://doi.org/10.1007/s00125-020-05180-x</u> .
48	31	27 LiC Dong O Fong L LiF Viong N Ho O Clinical Characteristics of Diabotic Patients with
49	32	COVID-19 I Diabatos Ros 2020:2020:1652/03 https://doi.org/10.1155/2020/1652/03
50	52	COVID-17.5 Diabetes Res 2020,2020.1052405. <u>https://doi.org/10.1155/2020/1052405</u> .
51	33	28. Zhu L. She Z-G. Cheng X. et al. Association of Blood Glucose Control and Outcomes in Patients
52	34	with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020: 31: 1068-1077.e3.
53 51		0 71
54	35	29. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type
56	36	2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes
57	37	Endocrinol 2020;8:813-22. https://doi.org/10.1016/S2213-8587(20)30272-2.
58		
59	38	30. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients
60	39	infected with COVID-19: A systematic review. PLoS One 2020; 15: e0241955.

3 4 5	1 2	31. Elamari S, Motaib I, Zbiri S, et al. Characteristics and outcomes of diabetic patients infected by the SARS-CoV-2. Pan Afr Med J; 37. Epub ahead of print 2020. DOI: 10.11604/pamj.2020.37.32.25192.
6 7	3	32 . Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid 10 with diabates RML Open Diabates Res Care 2020; 8: e001242
8 9 10	+ 5	33 Tian W Jiang W Yao L et al. Predictors of mortality in hospitalized COVID-19 patients: A
10 11 12	6	systematic review and meta-analysis. J Med Virol 2020; 92: 1875–1883.
13 14 15	7 8	34. Carlson N, Nelveg-Kristensen K -E., Freese Ballegaard E, et al. Increased vulnerability to COVID-19 in chronic kidney disease. J Intern Med 2021; joim.13239.
16 17 18	9 10	35 . Portolés J, Marques M, López-Sánchez P, et al. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. Nephrol Dial Transplant 2020; 35: 1353–1361.
19 20 21 22 23	11 12 13	36 . Leon-Abarca JA, Memon RS, Rehan B, et al. The impact of COVID-19 in diabetic kidney disease and chronic kidney disease: A population-based study. medrxiv. Epub ahead of print 2020. DOI: <u>https://doi.org/10.1101/2020.09.12.20193235</u> .
24 25 26 27	14 15 16	37 . Lazarus G, Audrey J, Wangsaputra VK, et al. High admission blood glucose independently predicts poor prognosis in COVID-19 patients: A systematic review and dose-response meta-analysis. <i>Diabetes Res Clin Pract</i> 2021; 171: 108561.
28 29 30	17 18	38. Alahmad B, Al-Shammari AA, Bennakhi A, et al. Fasting Blood Glucose and COVID-19 Severity: Nonlinearity Matters. Diabetes Care 2020; 43: 3113–3116.
31 32 33	19 20	39. Chen L, Sun W, Liu Y, et al. Association of Early-Phase In-Hospital Glycemic Fluctuation With Mortality in Adult Patients With Coronavirus Disease 2019. Diabetes Care 2021; dc200780.
34 35 36 37	21 22 23	40 . Kapoor R, Timsina LR, Gupta N, et al. Maintaining Blood Glucose Levels in Range (70–150 mg/dL) is Difficult in COVID-19 Compared to Non-COVID-19 ICU Patients—A Retrospective Analysis, I Clin Med 2020; 9: 3635.
38 39 40	24 25	41. Shen Y, Fan X, Zhang L, et al. Thresholds of Glycemia and the Outcomes of COVID-19 Complicated With Diabetes: A Retrospective Exploratory Study Using Continuous Glucose
41 42 43	26 27	Monitoring. Diabetes Care 2021; dc201448.
 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 	21	

Characteristic	DM	Non _DM	p-valu
	N=448	N=1621	
Age, mean (SD), years	71.7 (11.9)	66.6 (16.3)	< 0.00
Age, median (P25, P75), years	72.0 (64.0; 80.0)	67.0 (55.0; 79.0)	< 0.00
Gender (male), n (%)	304 (67.9)	950 (58.6)	< 0.00
Glucose, mean, (SD)			
mg/dL	168 (74.4)	112 (24.8)	< 0.00
mmol/L	9.3 (4.1)	6.2 (1.4)	
Comorbidities, n (%)			
Hypertension	224 (50.0)	427 (26.3)	< 0.00
Hyperlipidaemia	154 (34.4)	255 (15.7)	< 0.00
Obesity	45 (10.0)	72 (4.44)	< 0.00
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)	0.00
Chronic kidney disease	30 (6.70)	46 (2.84)	< 0.00
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

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

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

SD, standard deviation







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

491x163mm (96 x 96 DPI)



In-hospital death 🛛 🔶 In-hospital death or IMV

Odds Ratio

In-hospital death or IMV

Charac

-

-

Odds Ratio

Characteristic increases the risk

In-hospital death

Odds ratio (95% CI); P-value

2.12 (1.014-4.5); p=0.046

2.14 (1.1-4.2); p=0.029

1.12 (1.08–1.2); p<0.001

1.08 (1.05–1.1); p<0.001

2.84 (1.1-8.1); p=0.05

3.14 (1.2-8.5); p=0.024

Odds ratio (95% CI); P-value

2.11 (1.5-2.9); p<0.001

1.70 (1.3-2.3); p<0.001

1.10 (1.08- 1.11); p<0.001 1.06 (1.05-1.1); p<0.001

2.96 (1.7-5.3); p<0.001

1.94 (1.03-3.7); p=0.039

2.14 (1.1-4.0); p=0.018 1.93 (1.1-3.6); p=0.026

2.30 (1.4-3.8); p<0.001

A. Subjects with diabetes

Mai

Ag

Obasit

CVI

н

СКЕ

COPI

B. Subjects without diabetes

٠

Mai

Age

Obesit

CVD

СКЕ

COPI







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

219x323mm (96 x 96 DPI)

400

600

600



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 Gratacòs¹, Xavier Cos-Claramunt ^{1,7}, Manel Mata-Cases ^{1,8,10}, Ramon Puig- Treserra¹, 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*}

TABLE OF CONTENTS			
		PAGE	
Supplementary Figure 1	Flow chart of the patients included in the study	2	
Supplementary Table 1	Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus	3	
Supplementary Figure 2.	Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).	5	
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		
Supplementary Table 3.	Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.	7	
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).		
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).	9	
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.	10	







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 m ²	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

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

to occure with





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

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
BMJ Open

		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

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

> 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	V		0.240	
p<0.05 ** p<0.01 *** p<0.001				-n/	>	

BMJ Open

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		O_{h}	0.190	
p<0.05 ** p<0.01 *** p<0.001				T	,	

2	
3	
4	
5	
5	
0	
/	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	

1

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 I	nvasive mechanical v	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	5		0.188
p<0.05 ** p<0.01 *** p<0.001						

 BMJ Open

	ST	ROBE 2007 (v4) Statement—Checklist of items that should be included in reports of <i>cross-sectional studies</i>	
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			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	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	(<i>a</i>) 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		<u> </u>	
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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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.

..ist item and , .vailable on the Web sit .www.epidem.com/). Information c

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-051237.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jun-2021
Complete List of Authors:	Ortega, Emilio; Hospital Clinic de Barcelona Corcoy, Rosa; Hospital de la Santa Creu i Sant Pau, Gratacòs , Mònica; IDIAP Jordi Gol Cos Claramunt, Francesc Xavier; IDIAP Jordi Gol Mata-Cases, Manel; IDIAP Jordi Gol, DAP-Cat Group, Unitat de Suport a la Recerca Barcelona; Institut Catala De La Salut, La Mina Primary Health Care Centre Puig- Treserra, Ramon ; IDIAP Jordi Gol Real, Jordi; Institut Universitari d'Investigaci Primaria Jordi Gol (IDIAP Jordi Gol), DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat Vlacho, Bogdan; IDIAP Jordi Gol Castelblanco, Esmeralda; Hospital de la Santa Creu i Sant Pau, Endocrinology Domingo, Pere; Hospital de la Santa Creu i Sant Pau, Infectious Diseases Khunti, Kamlesh; University of Leicester, Diabetes Research Centre Franch-Nadal, Josep; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut Mauricio, Didac ; Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutriton; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutriton; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Didac Mauricio
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	COVID-19, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < INFECTIOUS DISEASES



- /



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1		
2		
3 1	1	Risk factors for severe outcomes in people with
4 5		
6	2	diabetes hospitalized for COVID-19: A cross-
7 8	3	sectional "Covid Data Save Lives" database study
9 10	4	Emilio Ortega ^{1,2,3} , Rosa Corcoy ^{4,5,6} , Mònica Gratacòs ¹ , Xavier Cos-Claramunt ^{1,7} , Manel Mata-
11	5	Cases ^{1,8,10} , Ramon Puig- Treserra ¹ , Jordi Real ¹ , Bogdan Vlacho ¹ , Esmeralda Castelblanco ^{1,8} , Pere
12	0	Domingo ⁵ , Kamiesh Khunti ¹¹ , Josep Franch-Nadal ^{10,12,*} and Didac Mauricio ^{11,0,10,*}
13	7	
14	8	¹ DAP-Cat group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la recerca a
15	9	l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
16	10	² CIBER of physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III
17	11	(ISCIII), Spain
18	12	³ Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi i Suñer,
19	13	Hospital Clinic, Barcelona, Spain
20	14	⁴ Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau;
21	15	⁵ Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
22	16	⁶ CIBER of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Instituto de Salud Carlos III
23	17	(ISCIII), Spain
24	18	⁷ Innovation office at Institut Català de la Salut, Barcelona, Spain
25	19	⁸ CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII),
26	20	Spain
27	21	9 Infectious Diseases, Hospital Universitari de la Santa Creu i Sant Pau, Institut de Recerca Hospital
28	22	Universitari de la Santa Creu i Sant Pau. Snain
29	$\frac{1}{23}$	¹⁰ Primary Health Care Center La Mina, Gerència d'Àmhit d'Atenció Primària Barcelona Ciutat, Institut
30	$\frac{23}{24}$	Català de la Salut Sant Adrià de Besõe Spain
31	25	¹¹ Diabatos Research Contro. University of Leisester Leisester UK
32	$\frac{23}{26}$	¹² Primary Health Care Conter Payal Sud Cordonia d'Atonció Primaria. Institut Català de la Salut Barcelona
33	20	Crasin
34	27	Spain ¹³ Demontrary of Madigina University of Via, Control University of Catalania Via Bassalana Casia
35	20	Departament of Medicine, University of Vic - Central University of Catalonia, Vic, Barcelona, Spain.
36	29	
37	30	
38	31	*Corresponding authors
39	32	Dr Dídac Mauricio,
40	33	Hospital de la Santa Creu i Sant Pau,
41	34	Sant Quintí, 89
42	35	08041 Barcelona, Spain
43	36	Telephone No.: +34 935565661; Fax No.: +34 9355602
44	37	Email: didacmauricio@gmail.com
45	38	<u>_</u>
46	39	Dr Josep Franch-Nadal.
47	40	Centre d'Atenció Primària Raval Sud
48	41	Av Drassanes 17-21
49	42	08001 Barcelona Snain
50	43	Telephone No \cdot +34 933294495 · Fax No \cdot +34 9344277 63
51	$\frac{1}{4}$	Empil: ioson franch@gmpil.com
52	44 45	Eman. josep.trancn@gman.com
53	ч Ј 16	
54	40 17	Mand seconds all stars at 201, an aire texts 2/22
55	4/ 10	vvora count: adstract 291; main text 3623
56	40	Tables: 1
57	49 50	Figures: 6
58	50	Keterences: 46
59	51	Appendix: Tables 7; Figures 1;
60		

1 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 8 associated with mortality and the composite of mortality or invasive mechanical ventilation (IMV) 9 in the overall population, and stratified for the presence or absence of DM. Spline analysis was 10 conducted on the entire population to investigate the relationship between glucose levels at 11 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

Page 5 of 48

1

BMJ Open

2		
3 4	1	function. Moreover, hyperglycaemia on admission was strongly associated with poor outcomes,
5	2	suggesting that personalised optimisation could help to improve outcome during the hospital
7		
8 9	3	stay.
10		
11 12	4	Keywords: COVID-19, Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation
13	5	
14 15	ſ	
16	6	Strengths and limitations of this study
17 18		
19	7	• A major strength of our study is the thorough methodological approach to analyse the risk
20 21	8	of in-hospital COVID-19-related complications based on the presence of DM or overt
22	0	of in hospital COVID 17 felated completations based on the presence of Divior overt
23 24	9	hyperglycaemia.
25		
26 27	10	• We were limited by not having access to the patients' medical history prior to admission,
28	11	
29 30	11	and the low number of registers for some important DM variables (such as HbIAc), and the
31	12	lack of data on weight or BMI (only the presence of obesity).
32 33		
34	13	• The selection of DM subjects was made based on a proxy algorithm (including DM
35 36		
37	14	diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose
38 39	15	levels at admission.
40		
41 42	16	• We used random blood glucose on admission for spline analyses, thus preventing the
43	10	• We used fundom blood glucose on admission for spine analyses, thus preventing the
44 45	17	distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.
46		
47 48	18	
49		
50 51		
52		
53 54		
55		
56 57		
58		
59 60		
00		

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

BMJ Open

3
4
5
6
7
8
0 0
9 10
10
11
12
13
14
15
16
17
18
19
20
20
∠ I วา
22
23
24
25
26
27
28
29
30
31
27
32
33
34
35
36
37
38
39
40
41
יד ⊿ר
-⊤∠ ⁄10
45
44
45
46
47
48
49
50
51
52
52
57
54
55 56
56
57
58
59
60

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.

7 Previous studies have reported that people with DM are prone to new infections and recurrence, 8 particularly influenza and pneumonia, due to impaired defences and disease complications [13-16]. 9 Although the estimated prevalence of DM in COVID-19 infected patients varies greatly by 10 geographical region, it is considered similar to the DM prevalence in the general population, thus 11 not representing a risk factor for infection [17]. However, the prevalence of diabetes among COVID-12 19 hospitalized subjects is higher than the overall diabetes prevalence [17, 18]. A study conducted in 13 England found that a third of in-hospital deaths occurred in people with type 2 DM and that these 14 patients had greater odds of COVID-19-related in-hospital death than those without DM [19]. This 15 observation has been confirmed in a meta-analysis showing that DM is associated with a 2-fold 16 higher risk of dying from COVID-19 [20], and a second study reporting that patients with pre-17 existing DM have a 3-fold greater risk of in-hospital mortality [21]. 18 Early reports showed that about half of patients with severe COVID-19 presented acute 19 hyperglycaemia, with no more than 10% of them having a prior diagnosis of DM [22, 23]. Following 20 these observations, two meta-analyses concluded that hyperglycaemia at hospital admission is 21 associated with severe complications and mortality, regardless of diabetes status [24,25]. Moreover,

22 hyperglycaemia also has a negative impact on the therapeutic response to tocilizumab in patients

23 with COVID-19-related systemic inflammation [26].

In Spain, DM is a highly prevalent disease in people over 18 years of age (13.8% of the population) <text><text><text><text> [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.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

 BMJ Open

1 2. Methods

2.1 Study design and settings

3	This was a cross-sectional study in hospitalized individuals infected with SARS-CoV-2, stratified by
4	presence or absence of DM. Data were obtained from pseudonymized electronic health records
5	provided by six general hospitals from the HM Hospitales group (Spain). The database included
6	information related during the hospital stay (diagnosis and procedures codes, prescribed
7	medications, vital signs, and laboratory parameters), from 2,310 subjects during the first COVID-19
8	wave with hospital admission between January 27 and April 24, 2020 (study start and end date,
9	respectively). Subjects were followed from admission to hospital discharge or death. Detailed
10	information related to the database is presented in the Supplementary material (Database
11	description).
12	The study data were collected by medical professionals of the HM Hospitales group (Spain) during
13	the first wave of the COVID-19 pandemic. In order to promote COVID-19 related research, the HM
14	Hospitales group pseudonymized the medical history of SARS-CoV-2 infected patients and created
15	a project titled: "Covid Data Save Lives". Before access was granted, a formal petition, specific
16	study protocol, and ethics committee approval were obtained. The study was approved by the
17	Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol,

19 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
 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.

5 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/m²], 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.

20 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 %).

BMJ Open

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
10	
17	
10	
20	
20	
27	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43 11	
44 15	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

1	The association between the study outcomes (i.e., mortality and mortality or mechanical
2	ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and
3	associated risk factors. In addition, several models of interest were tested (a model with basic
4	clinical variables such as age and sex, a model adding obesity, hypertension and hyperlipidaemia,
5	and a model adding organ lesion variables, such as CVD, heart failure, CKD, COPD), namely with
6	the sequential inclusion of different covariates and the estimated differences expressed as odds
7	ratio (OR) and the respective 95% confidence intervals (CI). We evaluated goodness of fit of the
8	logistic regression models with H&L test (Hosmer–Lemeshow test). To analyse the nonlinear
9	relationship of random blood glucose levels on admission with the two study outcomes, we used an
10	adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves
11	with two degrees of freedom (knots) using the mgcv package in R, version 1.8-31[29] with
12	adjustment for potential confounders. We analysed the entire database available and no statistical
13	power was calculated. Data management and statistical analyses were performed using the R
14	statistical software version 3.6.1 (<u>https://www.r-project.org/</u>).
15	2.5 Patient and Public Involvement

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

18 **3. Results**

19 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,

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 m² vs. 81.2±23.9 mL/min/1.73 m²; 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.

14 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

BMJ Open

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 \geq 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).

24 3.4. Factors associated with hospital death and death or IMV by comorbid diabetes

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).

21 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,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 15 of 48

1 2 3

BMJ Open

4	
5	
6	
7	
, 0	
0	
9	
10	
11	
12	
12	
13	
14	
15	
16	
17	
18	
10	
19	
20	
21	
22	
23	
24	
27	
25	
26	
27	
28	
29	
30	
20	
31	
32	
33	
34	
35	
26	
20	
37	
38	
39	
40	
<u>4</u> 1	
41 42	
42	
43	
44	
45	
46	
47	
۰, ۷۷	
40	
49	
50	
51	
52	
53	
55	
4 	
55	
56	
57	
58	
50	

60

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.

4 In our study, the proportion of severe COVID-19 cases (e.g., requiring IMV or ICU admission) in 5 the DM population was higher than in the non-DM cohort. Moreover, DM patients were more 6 frequently male and over 65 years, had more comorbid conditions, and higher levels of 7 inflammatory, endothelial, and coagulation dysfunction markers on admission. Different meta-8 analyses have reported that older age and male sex are characteristics associated with severe 9 COVID-19 infection and high fatality rates [17, 30, 31]. Along the same line, studies assessing the 10 phenotypic characteristics of COVID-19 patients with pre-existing DM have found that those with 11 severe infection were older, had more comorbidities (i.e., cerebrovascular disease, CVD, 12 hypertension, and COPD), and increased values of inflammation, endothelial and coagulation 13 dysfunction markers (e.g., D-dimer, procalcitonin, and thrombocytopenia), than those without DM 14 [30-35].

15 In our study, patients with DM had significantly higher creatinine on admission, lower eGFR, and 16 more frequently pre-existing CKD than non-DM subjects. Besides, CKD was the only comorbid 17 condition increasing the odds (three-fold increase) of in-hospital death (and death or IMV) among 18 the DM cohort after adjusting for age, sex, and confounding variables. Different meta-analyses have 19 identified CKD as a risk factor for severity and in-hospital death in SARS-CoV-2 infected patients 20 [7, 36-38]. Moreover, a recent study conducted in Danish hospital-diagnosed COVID-19 patients 21 reported that kidney insufficiency was independently associated with increased risk of severe 22 disease or death, and the degree of renal impairment inversely correlated with the rate of adverse 23 outcomes [39]. Although it is difficult to distinguish whether poor outcomes are linked to acute 24 kidney injury (AKI) developed during the course of the disease, or to pre-existing CKD [39], a study 25 conducted in Spain showed that patients with increased creatinine on admission, previous CKD, or

Page 16 of 48

2	
ر ۷	
т 5	
6	
7	
, 8	
0 0	
10	
11	
12	
12	
14	
15	
16	
17	
18	
19	
20	
21	
22	
22	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

1

1 developing AKI, had a higher risk of in-hospital death than those with normal creatinine on 2 admission [40]. Of note, the authors found that older age and diabetes, but not other comorbidities, 3 were associated with in-hospital death [40]. Finally, a study conducted in Mexico reported that, 4 patients with DM and CKD had a 2-fold higher rate of intubation, 56% higher ICU admission, and 5 21% excess probability of case-fatality once admitted, than subjects with CKD alone [41]. 6 In our study, we used splines as a scientific and preferable alternative to the categorization of BG 7 levels [42]. We used this approach because a recent dose-response meta-analysis demonstrated a 8 non-linear relationship between admission fasting blood glucose (FBG) level and COVID-19 9 severity, with high levels being significantly associated with increased mortality and poor outcome, 10 regardless of pre-existing DM [43]. These results confirmed previous observations that FBG on 11 admission, and the odds of being admitted to the ICU, followed a logarithmic association, with 12 different magnitudes of risk depending on the baseline level [42]. We add to the literature that, 13 besides the previously reported effect of hyperglycaemia on the risk of COVID-19 severity, ICU 14 admission, and mortality [24,25], BG has a non-linear relationship with case fatality and the risk of 15 death or IMV. It is possible that this relationship was also accompanied by, or reflected glycaemic 16 variability and less time spent in range. Indeed, glycaemic fluctuation has been reported to be 17 independently associated with poor prognosis and mortality in COVID-19 hospitalized patients 18 [44]. In the same vein, a study on ICU patients showed that the less time spent in range was 19 associated with increased utilization of a ventilator, prolonged mechanical ventilation, and 20 increased mortality [45]. Most importantly, a spline analysis of glucose levels in DM patients with 21 continuous glucose monitoring showed a non-linear relationship between time spent above range

23 (need for ICU admission, mechanical ventilation, or critical illness) [46].

24 4.1 Limitations of this study

22

and glycaemic variability with the increased likelihood of composite adverse COVID-19 outcomes

Page 17 of 48

1 2

BMJ Open

3
4
5
6
7
8
g
10
10
11
12
13
14
15
16
17
18
10
20
∠∪ ว1
∠ I 22
22
23
24
25
26
27
28
20
29
30
31
32
33
34
35
36
37
38
20
39
40
41
42
43
44
45
46
47
48
<u>10</u>
+7 50
50
51
52
53
54
55
56
57
58
50
27
60

1	The findings of this study must be interpreted with caution and a number of limitations should be
2	borne in mind. Firstly, we had limited data for SARS-CoV-2 infected persons. For instance, we did
3	not have access to the patient's medical history prior to admission; so the possibility exists that
4	some important medical conditions were not included in the emergency room medical report and,
5	therefore, not included in the analysis. Moreover, data on socio-demographic characteristics
6	(ethnicity, race, economic or educational status) and toxic habits (smoking, alcohol or drug use)
7	were not available. Secondly, we had very few registers for some important variables for diabetes,
8	such as Hb1Ac (data from only 36 patients) and no data on weight or BMI. Indeed, no more than
9	10% of the patients had documented obesity, which is clearly lower than the expected prevalence in
10	the general population. This was most probably related to the clinician's under-recording for this
11	particular condition and to the fact that, during the first wave, obesity had not yet been identified as
12	a significant risk factor and thus not specifically registered. Thirdly, the selection of subjects with
13	DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay,
14	antidiabetic treatment, and HbA1c and blood glucose levels), which could have introduced
15	selection or referral bias, potentially leading to an inaccurate estimation of DM prevalence.
16	Fourthly, and inherent to data coming from hospital medical records, missing values could have
17	reduced the statistical power of the study, or produced biased estimates. Fifthly, we used random
18	BG on admission for the spline analyses, thus preventing the distinction between stress-related
19	hyperglycaemia and uncontrolled pre-existing DM. This also prevented the analysis of time in
20	range or BG variability, both being linked to increased severity, case fatality, and poor COVID-19
21	outcomes [42-46]. Lastly, the study period coincides with the height of the first pandemic wave in
22	Spain, when there was a shortage of ventilators and intensive care beds. At this point, age was the
23	deciding factor for whether or not someone received potentially life-saving ICU care. This might be
24	reflected in our results, where in-hospital death was more frequent among those over 65 years, but
25	ICU admission was more frequent among those ≤65 years.

1 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.

1 2		
3 4 5 6 7	1 2 3 4	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, X.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.
8 9 10 11 12 13	5 6 7 8 9 10	Acknowledgements: COVID DATA SAVE LIVES -Hospitales HM for providing database. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) and CIBER of physiopathology of obesity and Nutrition (CIBEROBN) are initiatives from the Instituto de Salud Carlos III, Madrid, Spain. The authors acknowledge Amanda Prowse (Lochside Medical communications Ltd.) for providing support in paper editing. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).
14 15	11	Funding: This study was supported by the Primary Care Diabetes Europe grant (grant number FEr20/0020)
16	12	Data availability: Data may be obtained from a third party and are not publicly available.
17 18 19	13 14	Conflicts of interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.
20 21	15 16	E.O. has received advisory and or speaking fees from Astra-Zeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Sanofi, and Amgen; they received research grants to the institution from MSD and Amgen.
22	17	R.C. has received advisory and/or speaking fees from Abbott, Ascensia, Lilly, MSD, Novo Nordisk and Sanofi.
24 25 26 27	18 19 20 21	M. M-C. has received advisory honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received speaker honoraria from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, Menarini, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi.
28 29 30 31	22 23 24	J. F-N has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.
32 33 34	25 26 27	K.K. has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen, and Napp
35 36 37 38	28 29 30	D. M. has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.
39 40 41 42	31 32 33 34	P. D. has received lecture and Advisory Board fees from Gilead Sciences, Roche, Merck, Sharp & Dohme, ViiV Healthcare, Janssen & Cilag, Theratechnologies, Boehringer Ingelheim, and Ferrer International. P.D. has received research grants from Gilead Sciences, ViiV Healthcare, GSK, Janssen & Cilag, and Boehringer Ingelheim.
43 44	35	B. V, X.C-C, J.R, R.P-T, M.G, and E.C. have no conflict of interest to declare.
45 46 47 48 49 50 51 52 53 54 55 56 57 58 59	36	
60		

2							
3	1	References					
4	1	Kerences					
5	2	1 World Health Organization 15-Novel Coronavirus(2019-nCoV) WHO Bull 2020: 1–7					
6	-	i vona neural organization. 10 nover coronaviras/2019 neov j. virio Ban 2020, 1 7.					
/	3	2. Agència de Salut Pública de Catalunya (ASPCAT). Informe tècnic resum dels casos de covid-19 a					
8 0	4	Catalunya					
9 10	5	http://salutpublica.gencat.cat/web/.content/minisite/aspcat/butlletins/vigilanciaaspcat/2020/45/INF					
10	6	ORME_TECNIC_3_COVID_19_020/20_pdf (2020)					
12	0	OKIVIL-11ECIVIC-0-COVID-17_020420.pdf (2020).					
13	7	3 Linde Pablo (February 1, 2020) «Sanidad confirma en La Gomera el primer caso de coronavirus					
14	8	en España» El País ISSN 1134-6582 Consulted March 10 2020 Available from:					
15	9	https://elpais.com/sociedad/2020/01/31/actualidad/1580509404_469734.htm					
16	,	https://elpuis.com/sociedud/2020/01/01/detuandud/150050/404_40//04.htm					
17	10	4. Munivappa R. Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. American					
18	11	Journal of Physiology-Endocrinology and Metabolism 2020:318(5):E736-E741					
19							
20	12	5. Zhou Y, Yang O, Chi I, et al. Comorbidities and the risk of severe or fatal outcomes associated					
22	13	with coronavirus disease 2019: A systematic review and meta-analysis. Int I Infect Dis 2020: 99: 47–					
23	14	56					
24							
25	15	6. Deng G, Yin M, Chen X, et al. Clinical determinants for fatality of 44,672 patients with COVID-19.					
26	16	Crit Care 2020; 24: 179.					
27							
28	17	7. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, et al. Predictors of in-hospital COVID-19					
29	18	mortality: A comprehensive systematic review and meta-analysis exploring differences by age. sex					
30	19	and health conditions. PLoS One 2020; 15: e0241742.					
32							
33	20	8. Pendu J Le, Breiman A, Rocher J, et al. ABO Blood Types and COVID-19: Spurious, Anecdotal, or					
34	21	Truly Important Relationships? A Reasoned Review of Available Data. Viruses 2021;13:160.					
35	22	doi:10.3390/v13020160					
36							
37	23	9. Sardu C, Marfella R, Maggi P, et al. Implications of AB0 blood group in hypertensive patients					
38	24	with covid-19. BMC Cardiovasc Disord 2020;20:373. doi:10.1186/s12872-020-01658-z					
39 40							
41	25	10. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and					
42	26	TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271-280.e8.					
43	27	doi:10.1016/j.cell.2020.02.052					
44	•						
45	28	11. Baral R, Tsampasian V, Debski M, <i>et al</i> . Association Between Renin-Angiotensin-Aldosterone					
46	29	System Inhibitors and Clinical Outcomes in Patients With COVID-19. JAMA Netw Open					
47	30	2021;4:e213594. doi:10.1001/jamanetworkopen.2021.3594					
48 40	21						
49 50	22	12. Matarese A, Gambardella J, Sardu C, <i>et al.</i> mik-98 Regulates 1MPR552 Expression in Human					
51	32 22	Endothelial Cells: Key Implications for COVID-19. Biomedicines 2020;8:462.					
52	33	doi:10.3390/biomedicines8110462					
53	31	12 Papazafironoulou AK Antononoulos & The COVID 10 nondemic and dishetes melliter					
54	34	Archives of Modical Sciences, Athorogeleratic Discasses 2020/Ev200					
55	55	Archives of Medical Sciences. Ameroscierotic Diseases 2020;5:e200.					
56 57	36	14 McDonald HI Nitsch D Millett F. Sinclair A. Thomas SL. New actimates of the hurden of acute					
57 58	37	community-acquired infections among older neonle with dishetes mellitus: a retrospective schort					
59	38	study using linked electronic health records. Diabetic Med 2014;31(5):606-614					
60	20						

Page 21 of 48

1						
2						
4 5	1 2	15. Li S, Wang J, Zhang B, Li X, Liu Y. Diabetes mellitus and cause-specific mortality: a population- based study. Diabetes & metabolism journal 2019;43(3):319-341.				
6	3	16. Del Sole F. Farcomeni A. Loffredo L. Carnevale R. Menichelli D. Vicario T. <i>et al.</i> Features of				
/ 8	4	severe COVID-19: A systematic review and meta-analysis. Eur I Clin Invest 2020:50:0–1.				
9	5	https://doi.org/10.1111/eci.13378.				
10						
11	6	17. Pugliese G, Vitale M, Resi V, Orsi E. Is diabetes mellitus a risk factor for COronaVIrus Disease				
12	7	19 (COVID-19)? Acta Diabetol 2020;19. <u>https://doi.org/10.1007/s00592-020-01586-6</u> .				
15 14	0					
15	8	18. Peric S, Stulnig TM. Diabetes and COVID-19. Wien Klin Wochenschr 2020;132:356–61.				
16	9	doi:10.1007/s00508-020-01672-3				
17	10	19. Barron F. Bakhai C. Kar P. Weaver A. Bradley D. Ismail H. <i>et al.</i> Associations of type 1 and type				
18	11	2 diabetes with COVID-19-related mortality in England: a whole-population study. The Lancet				
20	12	Diabetes & Endocrinology 2020.				
21						
22	13	20. Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in				
23	14	hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol 2020.				
24 25	15	21 Martines A. Borne CD. Zhao M. Tarahar C. Dishatara and faster for any tar COVID 10				
26	15	21. Mantovani A, Byrne CD, Zheng M, Targner G. Diabetes as a risk factor for greater COVID-19				
27	10	severity and in-nospital death: A meta-analysis of observational studies. Nutrition, Metabolism and				
28	1 /	Cardiovascular Diseases 2020,50(0).1250-1240.				
29	18	22. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome				
30 31	19	and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern				
32	20	Med 2020;180:934-43.				
33						
34	21	23. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in				
35 36	22	Wuhan. J Allergy Clin Immunol 2020;146:110-8.				
37	23	24. Lee MH, Wong C, Ng CH, Yuen DCW, Lim AYL, Khoo CM. Effects of hyperglycaemia on				
38	24	complications of COVID-19: A meta-analysis of observational studies. Diabetes Obes Metab				
39	25	2021;23:287-9.				
40	26					
41 42	27	25. Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and				
43	28	severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep 2021;41.				
44	29	26 Marfella P. Paolissa P. Sardu C. et al. Nagative impact of hyperglycoomia on tacilizymah				
45	31	therapy in Covid-19 patients. Diabetes Metab 2020:46:403-5				
46 47	51	incrapy in covid-17 patients. Diabetes wetab 2020,40.400-0.				
47 48	32	27. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of				
49	33	diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia 2012;				
50	34	55(1):88-93.				
51	2.5					
52 53	35	28. Caballero AE, Ceriello A, Misra A, <i>et al.</i> COVID-19 in people living with diabetes: An				
54	36	international consensus. J Diabetes Complications 2020; 34: 107671.				
55	37	29 Wood S (2019) mgay: mixed CAM computation vehicle with automatic smoothness estimation				
56	38	R-package version 1.8–31. https://CRAN.R-project.org/package=mgcv				
57	50	represented to off https://ereinticeprojectiong/package https://				
58 59	39	30. Li G, Deng Q, Feng J, Li F, Xiong N, He Q. Clinical Characteristics of Diabetic Patients with				
60	40	COVID-19. J Diabetes Res 2020;2020:1652403. https://doi.org/10.1155/2020/1652403.				

3	1	31. Izcovich A. Ragusa MA. Tortosa F. et al. Prognostic factors for severity and mortality in patients					
4	2	infected with COVID-19: A systematic review. PLoS One 2020: 15: e0241955					
5	2	Intered with 60 vib 17.11 systemate review. 1 600 One 2020, 10. c0241700.					
6	3	22 Cariou B. Hadiadi S. Wargny M. Pichelin M. Al Salameh A. Alliy I. et al. Phonotypic					
7	1	sectoristics and programs of inpatients with COVID 10 and dishetees the COPONADO study					
8	4	characteristics and prognosis or inpatients with COVID-19 and diabetes: the COKONADO study.					
9	3	Diabetologia 2020;63:1500–15. <u>https://doi.org/10.1007/s00125-020-05180-x</u> .					
10	(
11	6	33. Zhu L, She Z-G, Cheng X, <i>et al.</i> Association of Blood Glucose Control and Outcomes in Patients					
12	/	with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020; 31: 1068-1077.e3.					
13	0						
15	8	34. Elamari S, Motaib I, Zbiri S, <i>et al.</i> Characteristics and outcomes of diabetic patients infected by					
15	9	the SARS-CoV-2. Pan Afr Med J; 37. Epub ahead of print 2020. DOI: 10.11604/pamj.2020.37.32.25192.					
17							
18	10	35. Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-					
19	11	19 with diabetes. BMJ Open Diabetes Res Care 2020; 8: e001343.					
20							
21	12	36. Laguna-Goya R, Utrero-Rico A, Talayero P, et al. IL-6–based mortality risk model for					
22	13	hospitalized patients with COVID-19. J Allergy Clin Immunol 2020; 146: 799-807.e9.					
23							
24	14	37. Working group for the surveillance and control of COVID-19 in Spain. Redondo-Bravo L, <i>et al.</i>					
25	15	The first wave of the COVID-19 pandemic in Spain: characterisation of cases and risk factors for					
26	16	severe outcomes, as at 27 April 2020. Eurosurveillance 2020:25:2001431. doi:10.2807/1560-					
27	17	7917 FS 2020 25 50 2001431					
28	1 /	7717.10.2020.20.001401					
29	18	38 Tian W. Jiang W. Vao I. <i>et al.</i> Predictors of mortality in hospitalized COVID-19 patients: A					
30	10	overtemetic review and mote analysis. I Mod Viral 2020; 02: 1975, 1992					
31	17	systematic review and meta-analysis. J wed virol 2020, 92. 10/3–1003.					
32	20	20 Carlson N. Nelvog Kristonson K. E. Freese Ballogaard F. <i>et al.</i> Increased vulnerability to					
33	20	COVID 10 in changing hidroge disease Lintern Med 2021 ising 12220					
34 25	<i>L</i> I	COVID-17 III CHOILIC KIULEY UISEase. J IIITEITI WEU 2021; JOIII. 15259.					
30	าา	40 Partolás I. Margues M. Lánaz Cánakoz P. et al. Chronis Lidney disease and exete hidronyinium					
30	22	40. Fortoles J, Marques M, Lopez-Sanchez F, et al. Chronic kidney disease and acute kidney injury					
38	23	in the COVID-19 Spanish outbreak. Nephrol Dial Transplant 2020; 35: 1353–1361.					
39	24						
40	24	41 . Leon-Abarca JA, Memon RS, Rehan B, <i>et al.</i> The impact of COVID-19 in diabetic kidney disease					
41	25	and chronic kidney disease: A population-based study. medrxiv. Epub ahead of print 2020. DOI:					
42	26	https://doi.org/10.1101/2020.09.12.20193235.					
43							
44	27	42. Alahmad B, Al-Shammari AA, Bennakhi A, <i>et al</i> . Fasting Blood Glucose and COVID-19 Severity:					
45	28	Nonlinearity Matters. Diabetes Care 2020; 43: 3113–3116.					
46							
47	29	43. Lazarus G, Audrey J, Wangsaputra VK, et al. High admission blood glucose independently					
48	30	predicts poor prognosis in COVID-19 patients: A systematic review and dose-response meta-					
49	31	analysis. Diabetes Res Clin Pract 2021; 171: 108561.					
50							
51	32	44. Chen L, Sun W, Liu Y, et al. Association of Early-Phase In-Hospital Glycemic Fluctuation With					
52	33	Mortality in Adult Patients With Coronavirus Disease 2019. Diabetes Care 2021; dc200780.					
53							
54	34	45. Kapoor R, Timsina LR, Gupta N, <i>et al</i> . Maintaining Blood Glucose Levels in Range (70–150					
55	35	mg/dL) is Difficult in COVID-19 Compared to Non-COVID-19 ICU Patients – A Retrospective					
50 57	36	Analysis I Clin Med 2020: 9: 3635					
57 50	20	1 mary 510. J. Chirt Hick 2020/ 7. 0000.					
59							
60							

1		
2		
4	l	46. Shen Y, Fan X, Zhang L, et al. Thresholds of Glycemia and the Outcomes of COVID-19
5	2	Complicated With Diabetes: A Retrospective Exploratory Study Using Continuous Glucose
6	3	Monitoring. Diabetes Care 2021; dc201448.
7		
8	4	
9	5	
10	·	
11		
12		
13		
15		
16		
17		
18		
19		
20		
∠1 22		
22		
24		
25		
26		
27		
28		
29 30		
31		
32		
33		
34		
35		
30 37		
38		
39		
40		
41		
42		
43 11		
45		
46		
47		
48		
49		
50 51		
51 52		
53		
54		
55		
56		
57		
58 50		
59 60		
00		

Characteristic	Overall study population N=2069	Diabetes N=448	No diabetesN=1 621	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	124 (47.7)	168 (74.4)	112 (24.8)	< 0.001
mmol/L	6.8(2.6)	9.3 (4.1)	6.2 (1.4)	
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

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

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

Figure legend/caption

1		
2		
3	1	
4	2	Eleven 1 Elevenhaut dis energy
5	2	rigure 1. Flowchart diagram
6	3	
7	4	Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.
8	5	
9	6	Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care
10	7	unit: IMV invasive mechanical ventilation *** $p < 0.001 \cdot ** p < 0.01 \cdot * p < 0.05$
11	8	and, mit, mit voite meetiamear ventilation. p (0.001, p (0.01, p (0.00)))
12	0	
13	0	
14	9	Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and
15	10	the composite outcome of death or invasive mechanical ventilation
16	10	the composite of death of invasive internation ventilation.
17		
18	11	Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD,
19	10	
20	12	cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical
21	12	ventilation
22	15	ventilation
23		
24	14	Figure 4 . Clinical and demographic variables associated with increased risk of in-hospital death and
25		
25	15	the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes
20	17	
27	16	(A) and without diabetes (B).
20		
30	17	Lagand: CKD, chronic kidney disease: COPD, chronic obstructive nulmonary disease: CVD
30	17	Legend. CRD, chronic Runey disease, COLD, chronic obstructive pullionary disease, CVD,
27	18	cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical
22		
31	19	ventilation
25		
26	20	Figure 5. Spline plot demonstrating a marked non-linearity in the relationship between plasma
30 27	21	glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive
27 20	22	mechanical ventilation (IMV) rate (B) Tick marks above the horizontal axis indicate the values at
20	23	which the observations were made. The dotted lines represent the 95% confidence interval. The
39	23	which the observations were made. The dotted lines represent the 50% confidence interval. The
40	24	model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD,
41	25	and COPD.
42		
43	26	Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure;
44	27	
45	27	CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease
46		
47	28	Figure 6. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized
48	29	smoothing splines. The shaded area represents the 95% confidence interval. The model was
49	30	adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD
50	31	
51	32	Logand: IMV intensive mechanical ventilation: CVD cardiovaccular diseases: HE heart failure:
52	22	CVD sknowie hidrose diesesse CODD sknowie skatusties walker as 1'
53	23 21	CKD, chronic klaney disease; COPD, chronic obstructive pulmonary disease
54	34	
55	36	
56	37	
57	38	
58	39	
59	40 71	
60	71	

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).

to beet terien only

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









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

491x163mm (96 x 96 DPI)


BMJ Open



58 59



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 crosssectional "Covid Data Save Lives" database study

Emilio Ortega ^{1,2,3}, Rosa Corcoy ^{4,5,6}, Mònica Gratacòs¹, Xavier Cos-Claramunt ^{1,7}, Manel Mata-Cases ^{1,8,10}, Ramon Puig- Treserra¹, 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*}

	TABLE OF CONTENTS	
		PAGE
Supplementary Table 1	Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus	2
Supplementary Figure 1.	Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).	4
Supplementary Table 2.	Number of events in patients with pre-existing diabetes and stress hyperglycaemia/unknown diabetes.	5
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.	6
Supplementary Table 4.	Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.	7
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).	8
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).	9
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.	10
Supplementary text	Database description.	11

4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
25
20
27
20
30
30
27
J∠ 22
22 24
24 25
22
30 27
رد د د
38
39
40
41
42
43
44
45
46
4/
48
49
50
51
52
53
54
55
56
57
58
59
60

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	X		
Renal function			
Glomerular filtration (CKD-EPI), mean (SD), mL/min/1.73 m ²	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		\bigcirc	
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), x10 ³ /µL	8.91 (6.52)	7.47 (4.17)	< 0.001
Platelets, mean (SD), x10³/µL	247 (112)	250 (116)	0.705

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			
CO2 pressure, mean (SD), mmHg	37.8 (9.95)	35.8 (7.42)	0.007
O2 pressure , mean (SD), mmHg	73.4 (35.4)	67.5 (30.9)	0.216
O2 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.

ore teries only

31.6

DM and >65 years



Α

50

40

30-

33.0



DM and ≤65 years

35.2

21.1



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

 BMJ Open

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

Kor -	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%)

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

BMJ Open

		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

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

> 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	V		0.240	
p<0.05 ** p<0.01 *** p<0.001				-n/	•	

 BMJ Open

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		$O_{\mathbf{b}}$	0.190	
p<0.05 ** p<0.01 *** p<0.001				T		

2	
3	
Δ	
5	
6	
7	
/ 0	
ð	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
27	
20	
29	
20	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	

1

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

		Death		Death or In	nvasive mechanical v	rentilation
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	·			N		

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

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

Page 45 of 48

BMJ Open

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	er revie	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					
		For peer review only - h	ttp://bmjopen.bmj.com/site	e/about/guidelines.xhtml	

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

Data sources/	8	For each variable of interest,			Page 7
measurement		give sources of data and details			Lines:12-16
		of methods of assessment			
		(measurement).			
		Describe comparability of			
		assessment methods if there is			
		more than one group			
Bias	9	Describe any efforts to address			Page 9
		potential sources of bias			Lines:1-7
Study size	10	Explain how the study size was			NA
2		arrived at			
Quantitative	11	Explain how quantitative			Page 8
variables		variables were handled in the			Lines:21-24
		analyses. If applicable, describe			
		which groupings were chosen,			
		and why	0		
Statistical	12	(a) Describe all statistical	N/A		Page 8
methods		methods, including those used to	6		Lines:21-24
		control for confounding			Page 9
		(b) Describe any methods used			Lines: 1-12
		to examine subgroups and			
		interactions			
		(c) Explain how missing data		1.	
		were addressed			
		(d) <i>Cohort study</i> - If applicable,			
		explain how loss to follow-up			
		was addressed			
		<i>Case-control study</i> - 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			

		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.	Page 7 Lines:12-18
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage			2	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 (<i>e.g.</i>, 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 	evie	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , 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 (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data 			Page 10 Lines:1-11

		(c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i> , average and total amount)		
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over timeCase-control study - Report numbers in each exposure category, or summary measures of exposureCross-sectional study - Report numbers of outcome events or 		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 	rien only	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
	10	Discuss limitations of the study	PECOPD 10 1: Discuss the	Page 1/

		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	2		Page 16 Lines:1-10
Other Information	n				
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	616	4	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.

*Checklist is protected under Creative Commons Attribution (<u>CC BY</u>) license.

BMJ Open

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-051237.R2
Article Type:	Original research
Date Submitted by the Author:	29-Jun-2021
Complete List of Authors:	Ortega, Emilio; Hospital Clinic de Barcelona Corcoy, Rosa; Hospital de la Santa Creu i Sant Pau, Gratacòs , Mònica; IDIAP Jordi Gol Cos Claramunt, Francesc Xavier; IDIAP Jordi Gol Mata-Cases, Manel; IDIAP Jordi Gol, DAP-Cat Group, Unitat de Suport a la Recerca Barcelona; Institut Catala De La Salut, La Mina Primary Health Care Centre Puig- Treserra, Ramon ; IDIAP Jordi Gol Real, Jordi; Institut Universitari d'Investigaci Primaria Jordi Gol (IDIAP Jordi Gol), DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat Vlacho, Bogdan; IDIAP Jordi Gol Castelblanco, Esmeralda; Hospital de la Santa Creu i Sant Pau, Endocrinology Domingo, Pere; Hospital de la Santa Creu i Sant Pau, Infectious Diseases Khunti, Kamlesh; University of Leicester, Diabetes Research Centre Franch-Nadal, Josep; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut Mauricio, Didac ; Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutrition; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutriton; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Endocrinology & Nutriton; Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau, Didac Mauricio
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology, Infectious diseases
Keywords:	COVID-19, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < INFECTIOUS DISEASES





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

2 3		
4	1	Risk factors for severe outcomes in people with
5 6	2	diabetes hospitalized for COVID-19: A cross-
7 8	3	sectional "Covid Data Save Lives" database study
9 10	4	Emilio Ortega ^{1,2,3} , Rosa Corcoy ^{4,5,6} , Mònica Gratacòs ¹ , Xavier Cos-Claramunt ^{1,7} , Manel Mata-
10	5	Cases ^{1,8,10} , Ramon Puig- Treserra ¹ , Jordi Real ¹ , Bogdan Vlacho ¹ , Esmeralda Castelblanco ^{1,8} , Pere
12	6	Domingo ⁹ , Kamlesh Khunti ¹¹ , Josep Franch-Nadal ^{1,8,12*} and Dídac Mauricio ^{1,4,8,13*}
13	7	
14	8	¹ DAP-Cat group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la recerca a
15	9	l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
16	10	² CIBER of physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III
17	11	(ISCIII), Spain
18	12	³ Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi i Suñer,
19	13	Hospital Clinic, Barcelona, Spain
20	14	⁴ Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau;
21	15	⁵ Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
23	16	⁶ CIBER of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Instituto de Salud Carlos III
24	l / 10	(ISCIII), Spain
25	18	⁷ Innovation office at Institut Catala de la Salut, Barcelona, Spain 8. CIPER - C Di la travel d'Associate d'Metaledia Disease (CIPERDEN). La titute de Cale de Cale du UCCUI)
26	20	CIBER OF Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII),
27	20	Span 9 Infactious Discascas Hagnital Universitari da la Santa Crou i Sant Pau Institut de Recerca Hagnital
28	$\frac{21}{22}$	Universitari de la Santa Creu i Sant Pau, Snain
29	$\frac{22}{23}$	¹⁰ Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat. Institut
30	24	Català de la Salut. Sant Adrià de Besòs. Spain
31	25	¹¹ Diabetes Research Centre, University of Leicester, Leicester, UK
32	26	¹² Primary Health Care Center Raval Sud, Gerència d'Atenció Primaria, Institut Català de la Salut, Barcelona,
33	27	Spain
34 25	28	¹³ Departament of Medicine, University of Vic - Central University of Catalonia, Vic, Barcelona, Spain.
36	29	
37	30	
38	31	*Corresponding authors
39	32	Dr Dídac Mauricio
40	33	Hospital de la Santa Creu i Sant Pau.
41	34	Sant Ouintí, 89
42	35	08041 Barcelona, Spain
43	36	Telephone No.: +34 935565661; Fax No.: +34 9355602
44	37	Email: <u>didacmauricio@gmail.com</u>
45	38	
46	39	Dr Josep Franch-Nadal,
47 70	40	Centre d'Atenció Primària Raval Sud,
40 49	41	Av. Drassanes, 17-21,
50	42	08001 Barcelona, Spain
51	43	Telephone No.: +34 933294495; Fax No.: +34 9344277 63
52	44	Email: <u>Josep.trancn@gmail.com</u>
53	46	
54	47	Word count: abstract 291: main text 3667
55	48	Tables: 1
56	49	Figures: 6
57	50	References: 46
58	51	Appendix: Tables 7; Figures 1;
59		
00		

1 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 8 associated with mortality and the composite of mortality or invasive mechanical ventilation (IMV) 9 in the overall population, and stratified for the presence or absence of DM. Spline analysis was 10 conducted on the entire population to investigate the relationship between glucose levels at 11 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

BMJ Open

3 4	1	function. Moreover, hyperglycaemia on admission was strongly associated with poor outcomes,
5 6	2	suggesting that personalised optimisation could help to improve outcome during the hospital
/ 8 9	3	stay.
10 11	4	Keywords: COVID-19, Diabetes, Hyperglycaemia, In-hospital mortality, Mechanical ventilation
12 13 14	5	
15 16	6	Strengths and limitations of this study
17		
18 19	7	• A major strength of our study is the thorough methodological approach to analyse the risk
20 21 22	8	of in-hospital COVID-19-related complications based on the presence of DM or overt
23 24	9	hyperglycaemia.
25		
26	10	• We were limited by not having access to the patients' medical history prior to admission.
27		
20 29 30	11	and the low number of registers for some important DM variables (such as Hb1Ac), and the
31 32 33	12	lack of data on weight or BMI (only the presence of obesity).
34 35	13	• The selection of DM subjects was made based on a proxy algorithm (including DM
36 37 20	14	diagnosis during the hospital stay, antidiabetic treatment, and HbA1c and blood glucose
39 40	15	levels at admission.
41		
42 43	16	• We used random blood glucose on admission for spline analyses, thus preventing the
44 45	17	distinction between stress-related hyperglycaemia and uncontrolled pre-existing DM.
46 47	18	
48		
49		
50 51		
52		
53		
54		
55		
56		
5/ 58		
58 59		
60		

1. Introduction

2	On January 30, 2020, the World Health Organization (WHO) declared the outbreak of the novel
3	SARS-CoV-2 coronavirus pandemic, a public health emergency of international importance. A few
4	days later, the respiratory disease caused by SARS-CoV-2 was officially named COVID-19 (Corona
5	Virus Infectious Disease 2019) [1, 2]. The first person diagnosed as positive in Spain was confirmed
6	on January 31, 2020, on the island of La Gomera [3]. The median age of hospitalized patients
7	infected with SARS-CoV-2 is 46.2 years, men comprise about 60% of patients, and the average
8	incubation period is 5.7 days [4]. As of February 8, 2021, approximately 3 million people have been
9	infected with SARS-CoV-2 in Spain since the start of the COVID-19 pandemic, and 62,295 persons
10	have died.
11	Conserved we are a server and that the weat servers and fatel as set of COVID 10 as our areas
11	Several meta-analyses have reported that the most severe and ratal cases of COVID-19 occur among
12	the elderly and in patients with underlying comorbidities [5-7]. Indeed, those with two or more
13	concomitant diseases have a significantly higher risk of admission to an intensive care unit (ICU),
14	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

BMJ Open

3
4
5
6
7
/
8
9
10
11
12
13
14
15
16
17
17
18
19
20
21
22
23
24
25
25
20
27
28
29
30
31
32
33
34
35
26
20
37
38
39
40
41
42
43
44
77 15
45
40
4/
48
49
50
51
52
53
57
54
55
56
57
58
59
60

23

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.

7 Previous studies have reported that people with DM are prone to new infections and recurrence, 8 particularly influenza and pneumonia, due to impaired defences and disease complications [13-16]. 9 Although the estimated prevalence of DM in COVID-19 infected patients varies greatly by 10 geographical region, it is considered similar to the DM prevalence in the general population, thus 11 not representing a risk factor for infection [17]. However, the prevalence of diabetes among COVID-12 19 hospitalized subjects is higher than the overall diabetes prevalence [17, 18]. A study conducted in 13 England found that a third of in-hospital deaths occurred in people with type 2 DM and that these 14 patients had greater odds of COVID-19-related in-hospital death than those without DM [19]. This 15 observation has been confirmed in a meta-analysis showing that DM is associated with a 2-fold 16 higher risk of dying from COVID-19 [20], and a second study reporting that patients with pre-17 existing DM have a 3-fold greater risk of in-hospital mortality [21]. 18 Early reports showed that about half of patients with severe COVID-19 presented acute 19 hyperglycaemia, with no more than 10% of them having a prior diagnosis of DM [22, 23]. Following 20 these observations, two meta-analyses concluded that hyperglycaemia at hospital admission is 21 associated with severe complications and mortality, regardless of diabetes status [24,25]. Moreover, 22 hyperglycaemia also has a negative impact on the therapeutic response to tocilizumab in patients

with COVID-19-related systemic inflammation [26].

BMJ Open

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.

<text><text><text><text>

 BMJ Open

1 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.

18 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

BMJ Open

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/m²], 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).

14 We considered the following variables as events or complications during the hospital stay: death,

15 acute respiratory distress syndrome (ARDS), pulmonary thrombosis, neurologic complications

16 (including encephalopathy, encephalitis, myelitis, and encephalomyelitis), thrombotic

17 complications identified by ICD-10 diagnostic codes (phlebitis and thrombophlebitis) admission to

18 ICU, and invasive mechanical ventilation (IMV) identified by ICD-10 procedure codes. The

19 composite primary outcome was defined as death or IMV.

20 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 %).

Page 11 of 49

BMJ Open

5 4	1	The association between the study outcomes (i.e., mortality and mortality or mechanical
5 6 7	2	ventilation) and DM was performed using logistic regression analyses adjusted for sex, age, and
7 8 9	3	associated risk factors. In addition, several models of interest were tested (a model with basic
10 11	4	clinical variables such as age and sex, a model adding obesity, hypertension and hyperlipidaemia,
12 13	5	and a model adding organ lesion variables, such as CVD, heart failure, CKD, COPD), namely with
14 15	6	the sequential inclusion of different covariates and the estimated differences expressed as odds
16 17 18	7	ratio (OR) and the respective 95% confidence intervals (CI). We evaluated goodness of fit of the
19 20	8	logistic regression models with H&L test (Hosmer-Lemeshow test). To analyse the nonlinear
21 22	9	relationship of random blood glucose levels on admission with the two study outcomes, we used an
23 24	10	adjusted semi-parametric model (generalized additive model [GAM]) calculating the spline curves
25 26 27	11	with two degrees of freedom (knots) using the mgcv package in R, version 1.8-31[29] with
28 29	12	adjustment for potential confounders. We analysed the entire database available and no statistical
30 31	13	power was calculated. Data management and statistical analyses were performed using the R
32 33 34	14	statistical software version 3.6.1 (<u>https://www.r-project.org/</u>).
35 36 37	15	2.5 Patient and Public Involvement
39 40	16	Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
41 42 43	17	plans of our research.
44 45 46	18	3. Results
47 48 49 50	19	3.1. Baseline Characteristics
50 51 52	20	Of the 2,306 subjects admitted to hospital within the period of study, 2,069 were over 18 years of
53 54	21	age and had a positive diagnostic test for SARS-CoV-2 (Figure 1). Among them, 448 (21.7%) were
55 56 57	22	identified as having DM and 1,621(78.3%) without DM (non-DM group). The characteristics of the
57 58 59	23	two populations at hospital admission are shown in Table 1 . Subjects with DM were on average 5.1
60	24	years older than non-DM subjects, and more frequently male (67.9% vs. 58.6%). Moreover,

BMJ Open

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 m² vs. 81.2±23.9 mL/min/1.73 m²; 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.

14 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

BMJ Open

2
2
3
4
5
6
7
/
8
9
10
11
11
12
13
14
15
10
16
17
18
19
20
20
21
22
23
2/
24
25
26
27
20
20
29
30
31
32
22
33
34
35
36
20
37
38
39
40
-т-О Л 1
41
42
43
44
45
45
46
47
48
10
49
50
51
52
52
54
55
56
57
57
20
59
60

1	was significantly higher among those ≤65 years and with DM, while age was not significant in those
2	without DM. When stratifying the results by sex, we did not observe differences except for
3	admission to ICU, which was significantly more frequent among male subjects with DM
4	(Supplementary Figure 1). Within the diabetes group, when we stratified by pre-existing DM (DM
5	codes and/or HBA1c ≥6.5% and/or antidiabetic treatment) and "stress" hyperglycaemia/ unknown
6	diabetes (glucose ≥200 mg/dl or insulin use within the first 24h period after admission), we
7	observed higher percentages for death, death or IMV, ARDS, admission to ICU and IMV events in
8	subjects with "stress" hyperglycaemia. The results of this stratification are presented in
9	Supplementary Table 2.
10	3.3. Baseline demographic and clinical characteristics associated with in-hospital death and death or IMV
11	For the overall hospitalized population, the demographic characteristics significantly associated
12	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–
13	1.11, respectively) (Figure 3; Supplementary Table 3). The comorbidities independently associated
14	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),
15	and COPD (OR=1.72, 95% CI=1.1–2.8).
16	When considering the composite outcome of death or IMV, the same variables associated with
17	death (i.e., age, sex, diabetes, CKD, and COPD) were identified as increasing the risk. In addition,
18	obesity emerged as an independently associated variable (OR=1.98, 95% CI=1.5–2.7) (Figure 3,
19	Supplementary Table 3).
20	The multiple logistic regression models were repeated to rule out the potential interaction of DM
21	with different clinical conditions (i.e., obesity, hyperlipidaemia, obesity and hyperlipidaemia, heart
22	failure, CKD, and COPD) for the in-hospital death outcome. The results showed that none of these
23	conditions affected the relationship between the risk of death and DM (Supplementary Table 4).

24 3.4. Factors associated with hospital death and death or IMV by comorbid diabetes
BMJ Open

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).

21 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,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 15 of 49

1 2 3

BMJ Open

4	
5	
6	
7	
/	
8	
9	
10	
11	
12	
13	
11	
15	
15	
10	
17	
18	
19	
20	
21	
22	
 22	
2J 74	
24	
25	
26	
27	
28	
29	
30	
31	
32	
22	
22	
34	
35	
36	
37	
38	
39	
40	
41	
 ⊿ว	
72 //2	
43	
44	
45	
46	
47	
48	
49	
50	
51	
57	
52	
55	
54 	
55	
56	
57	
58	
г 0	

60

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

4 In our study, the proportion of severe COVID-19 cases (e.g., requiring IMV or ICU admission) in 5 the DM population was higher than in the non-DM cohort. Moreover, DM patients were more 6 frequently male and over 65 years, had more comorbid conditions, and higher levels of 7 inflammatory, endothelial, and coagulation dysfunction markers on admission. Different meta-8 analyses have reported that older age and male sex are characteristics associated with severe 9 COVID-19 infection and high fatality rates [17, 30, 31]. Along the same line, studies assessing the 10 phenotypic characteristics of COVID-19 patients with pre-existing DM have found that those with 11 severe infection were older, had more comorbidities (i.e., cerebrovascular disease, CVD, 12 hypertension, and COPD), and increased values of inflammation, endothelial and coagulation 13 dysfunction markers (e.g., D-dimer, procalcitonin, and thrombocytopenia), than those without DM 14 [30-35].

15 In our study, patients with DM had significantly higher creatinine on admission, lower eGFR, and 16 more frequently pre-existing CKD than non-DM subjects. Besides, CKD was the only comorbid 17 condition increasing the odds (three-fold increase) of in-hospital death (and death or IMV) among 18 the DM cohort after adjusting for age, sex, and confounding variables. Different meta-analyses have 19 identified CKD as a risk factor for severity and in-hospital death in SARS-CoV-2 infected patients 20 [7, 36-38]. Moreover, a recent study conducted in Danish hospital-diagnosed COVID-19 patients 21 reported that kidney insufficiency was independently associated with increased risk of severe 22 disease or death, and the degree of renal impairment inversely correlated with the rate of adverse 23 outcomes [39]. Although it is difficult to distinguish whether poor outcomes are linked to acute 24 kidney injury (AKI) developed during the course of the disease, or to pre-existing CKD [39], a study 25 conducted in Spain showed that patients with increased creatinine on admission, previous CKD, or

BMJ Open

Page 16 of 49

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54 57	
55	
50 57	
5/ 50	
20	
29	

60

1 2

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].

6 In our study, we used splines as a scientific and preferable alternative to the categorization of BG 7 levels [42]. We used this approach because a recent dose-response meta-analysis demonstrated a 8 non-linear relationship between admission fasting blood glucose (FBG) level and COVID-19 9 severity, with high levels being significantly associated with increased mortality and poor outcome, 10 regardless of pre-existing DM [43]. These results confirmed previous observations that FBG on 11 admission, and the odds of being admitted to the ICU, followed a logarithmic association, with 12 different magnitudes of risk depending on the baseline level [42]. We add to the literature that, 13 besides the previously reported effect of hyperglycaemia on the risk of COVID-19 severity, ICU 14 admission, and mortality [24,25], BG has a non-linear relationship with case fatality and the risk of 15 death or IMV. It is possible that this relationship was also accompanied by, or reflected glycaemic 16 variability and less time spent in range. Indeed, glycaemic fluctuation has been reported to be 17 independently associated with poor prognosis and mortality in COVID-19 hospitalized patients 18 [44]. In the same vein, a study on ICU patients showed that the less time spent in range was 19 associated with increased utilization of a ventilator, prolonged mechanical ventilation, and 20 increased mortality [45]. Most importantly, a spline analysis of glucose levels in DM patients with 21 continuous glucose monitoring showed a non-linear relationship between time spent above range 22 and glycaemic variability with the increased likelihood of composite adverse COVID-19 outcomes 23 (need for ICU admission, mechanical ventilation, or critical illness) [46].

24 4.1 Limitations of this study

Page 17 of 49

1 2

BMJ Open

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
10	
יי סכ	
20 21	
ו∠ רכ	
22 วว	
ב∠ ∧ ר	
24 25	
25	
20	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
40 40	
50	
50 51	
ン 1 5 つ	
52 52	
57 23	
4כ רי	
55 57	
50 	
5/ 52	
58	
59	
៱៱	

1 The findings of this study must be interpreted with caution and a number of limitations should be 2 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 3 4 some important medical conditions were not included in the emergency room medical report and, 5 therefore, not included in the analysis. Moreover, data on socio-demographic characteristics 6 (ethnicity, race, economic or educational status) and toxic habits (smoking, alcohol or drug use) 7 were not available. Secondly, we had very few registers for some important variables for diabetes, 8 such as Hb1Ac (data from only 36 patients) and no data on weight or BMI. Indeed, no more than 9 10% of the patients had documented obesity, which is clearly lower than the expected prevalence in 10 the general population. This was most probably related to the clinician's under-recording for this 11 particular condition and to the fact that, during the first wave, obesity had not yet been identified as 12 a significant risk factor and thus not specifically registered. Thirdly, the selection of subjects with 13 DM was made based on a proxy algorithm (including DM diagnosis during the hospital stay, 14 antidiabetic treatment, and HbA1c and blood glucose levels), which could have introduced 15 selection or referral bias, potentially leading to an inaccurate estimation of DM prevalence. Besides, 16 we had no access to the patient's treatments prior to hospital admission. Since the proportion of 17 patients identified as having diabetes and receiving glucose-lowering agents was surprisingly low 18 (approximately 40%), this can be also attributed to antidiabetic treatment underreporting at 19 admission. Fourthly, and inherent to data coming from hospital medical records, missing values 20 could have reduced the statistical power of the study, or produced biased estimates. Fifthly, we 21 used random BG on admission for the spline analyses, thus preventing the distinction between 22 stress-related hyperglycaemia and uncontrolled pre-existing DM. This also prevented the analysis 23 of time in range or BG variability, both being linked to increased severity, case fatality, and poor 24 COVID-19 outcomes [42-46]. Lastly, the study period coincides with the height of the first 25 pandemic wave in Spain, when there was a shortage of ventilators and intensive care beds. At this 26 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.

1 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.

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.

Acknowledgements: COVID DATA SAVE LIVES -Hospitales HM for providing database. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) and CIBER of physiopathology of obesity and Nutrition (CIBEROBN) are initiatives from the Instituto de Salud Carlos III, Madrid, Spain. The authors acknowledge Amanda Prowse (Lochside Medical communications Ltd.) for providing support in paper editing. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).

Funding: This study was supported by the Primary Care Diabetes Europe grant (grant number FEr20/0020)

Data availability: Data may be obtained from a third party and are not publicly available.

Competing Interest: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

E.O. has received advisory and or speaking fees from Astra-Zeneca, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, Sanofi, and Amgen; they received research grants to the institution from MSD and Amgen.

R.C. has received advisory and/or speaking fees from Abbott, Ascensia, Lilly, MSD, Novo Nordisk and Sanofi.

M. M-C. has received advisory honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received speaker honoraria from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, Menarini, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi.

J. F-N has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.

K.K. has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen, and Napp

D. M. has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; they received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.

P. D. has received lecture and Advisory Board fees from Gilead Sciences, Roche, Merck, Sharp & Dohme, ViiV Healthcare, Janssen & Cilag, Theratechnologies, Boehringer Ingelheim, and Ferrer International. P.D. has received research grants from Gilead Sciences, ViiV Healthcare, GSK, Janssen & Cilag, and Boehringer Ingelheim.

B. V, FX.C-C, J.R, R.P-T, M.G, and E.C. have no conflict of interest to declare.

1		
2		
3 4	1	References
5 6	2	1. World Health Organization. 15-Novel Coronavirus(2019-nCoV). WHO Bull 2020; 1–7.
/ 8	3	2. Agència de Salut Pública de Catalunya (ASPCAT). Informe tècnic resum dels casos de covid-19 a
9	4	Catalunya,
10	5	http://salutpublica.gencat.cat/web/.content/minisite/aspcat/butiletins/vigilanciaaspcat/2020/45/INF
11	0	ORME-TECNIC-3-COVID-19_020420.pdf (2020).
12	7	2 Linds Bable (Educed 1 2020). Consided on General La Company de since de server de server de server de server
14	0	5. Linde, Fablo (February 1, 2020). «Sandad commina en La Gomera el primer caso de coronavirus
15	0	en España». El País, ISSN 1134-6382. Consulted March 10, 2020. Available from:
16	9	https://eipais.com/sociedad/2020/01/31/actualidad/1580509404_469734.htm
17	10	A Munivanna R Cubbi S COVID-19 nandomic coronaviruses and diabetes mellitus. American
18	10	Journal of Physiology Endogrinology and Metabolism 2020:318(5):E736-E741
19	11	Journal of Thysiology-Endocrinology and Metabolishi 2020,510(0).E750-E741.
20	12	5. Zhou Y. Yang O. Chi I. et al. Comorbidities and the risk of severe or fatal outcomes associated
21	13	with coronavirus disease 2019: A systematic review and meta-analysis. Int I Infect Dis 2020: 99: 47–
23	14	56.
24		
25	15	6. Deng G, Yin M, Chen X, et al. Clinical determinants for fatality of 44,672 patients with COVID-19.
26	16	Crit Care 2020; 24: 179.
27		
20 29	17	7. Mesas AE, Cavero-Redondo I, Álvarez-Bueno C, et al. Predictors of in-hospital COVID-19
30	18	mortality: A comprehensive systematic review and meta-analysis exploring differences by age, sex
31	19	and health conditions. PLoS One 2020; 15: e0241742.
32	• •	
33	20	8. Pendu J Le, Breiman A, Rocher J, et al. ABO Blood Types and COVID-19: Spurious, Anecdotal, or
34	21	Truly Important Relationships? A Reasoned Review of Available Data. Viruses 2021;13:160.
35	22	doi:10.3390/v13020160
30	22	0. Condu C. Marfalla D. Marai D. et al Ingligations of AD0 block and in boundary in structure
38	23	9. Sardu C, Martella K, Maggi P, et ul. Implications of Abb blood group in hypertensive patients
39	24	with covid-19. DMC Cardiovasc Disord 2020;20:373. doi:10.1186/\$12872-020-01658-2
40	25	10 Hoffmann M Kleine-Weber H Schroeder S <i>et al.</i> SARS-CoV-2 Cell Entry Depends on ACE2 and
41	26	TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020:181:271-280 e8
42	20	doi:10.1016/i.cell 2020.02.052
43 44	_,	
45	28	11. Baral R, Tsampasian V, Debski M, et al. Association Between Renin-Angiotensin-Aldosterone
46	29	System Inhibitors and Clinical Outcomes in Patients With COVID-19. JAMA Netw Open
47	30	2021;4:e213594. doi:10.1001/jamanetworkopen.2021.3594
48		
49	31	12. Matarese A, Gambardella J, Sardu C, et al. miR-98 Regulates TMPRSS2 Expression in Human
50	32	Endothelial Cells: Key Implications for COVID-19. Biomedicines 2020;8:462.
51	33	doi:10.3390/biomedicines8110462
52 53		
54	34	13. Papazafiropoulou AK, Antonopoulos S. The COVID-19 pandemic and diabetes mellitus.
55	35	Archives of Medical Sciences. Atherosclerotic Diseases 2020;5:e200.
56	26	
57	36	14 McDonald HI, Nitsch D, Millett E, Sinclair A, Thomas SL. New estimates of the burden of acute
58	5/	community-acquired infections among older people with diabetes mellitus: a retrospective cohort
59 60	38	study using linked electronic nealth records. Diabetic Med 2014;31(5):606-614.
00		

BMJ Open

2		
3	1	15 Li S Wang J Zhang B Li X Liu Y Diabetes mellitus and cause-specific mortality: a population-
4 5	2	based study. Diabetes & metabolism journal 2019;43(3):319-341.
6	3	16 Del Sola E Farcomeni A Loffredo L Carnevale R Menichelli D Vicario T <i>et al</i> Features of
7	1	10. Der Sole F, Farconierin A, Lonredo L, Carnevale K, Mericheni D, Vicano I, et al. Features of
8	4	severe COVID-19: A systematic review and meta-analysis. Eur J Clin Invest 2020;50:0–1.
9	3	https://doi.org/10.1111/eci.133/8.
10	6	17 Dealises C. Witch M. Deal V. Oral F. L. dishelse mulliture a sich faster for COmm Mary Discours
11	07	17. Pugliese G, Vitale M, Kesi V, Orsi E. Is diabetes mellitus a risk factor for COrona Virus Disease
12	/	19 (COVID-19)? Acta Diabetol 2020;19. <u>https://doi.org/10.100//s00592-020-01586-6</u> .
14	0	
15	8	18. Peric 5, Stulnig TM. Diabetes and COVID-19. Wien Klin Wochenschr 2020;132:356–61.
16	9	doi:10.1007/s00508-020-01672-3
17	10	
18	10	19. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, <i>et al.</i> Associations of type 1 and type
19	11	2 diabetes with COVID-19-related mortality in England: a whole-population study. The Lancet
20	12	Diabetes & Endocrinology 2020.
21		
22	13	20. Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in
23	14	hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol 2020.
24		
25	15	21. Mantovani A, Byrne CD, Zheng M, Targher G. Diabetes as a risk factor for greater COVID-19
26	16	severity and in-hospital death: A meta-analysis of observational studies. Nutrition, Metabolism and
2/	17	Cardiovascular Diseases 2020;30(8):1236-1248.
20		
30	18	22. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome
31	19	and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern
32	20	Med 2020;180:934-43.
33		
34	21	23. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in
35	22	Wuhan. J Allergy Clin Immunol 2020;146:110-8.
36	22	
37	23	24. Lee MH, Wong C, Ng CH, Yuen DCW, Lim AYL, Khoo CM. Effects of hyperglycaemia on
38	24	complications of COVID-19: A meta-analysis of observational studies. Diabetes Obes Metab
39	25	2021;23:287-9.
40	26	
41	27	25. Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and
42	28	severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep 2021;41.
45 44	29	
44 45	30	26. Marfella R, Paolisso P, Sardu C, et al. Negative impact of hyperglycaemia on tocilizumab
46	31	therapy in Covid-19 patients. Diabetes Metab 2020;46:403-5.
47		
48	32	27. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of
49	33	diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia 2012;
50	34	55(1):88-93.
51		
52	35	28. Caballero AE, Ceriello A, Misra A, et al. COVID-19 in people living with diabetes: An
53	36	international consensus. J Diabetes Complications 2020; 34: 107671.
54	-	
55	37	29. Wood S (2019) mgcy: mixed GAM computation vehicle with automatic smoothness estimation.
56	38	R-package version 1.8–31. https://CRAN.R-project.org/package=mgcv
57		r
58	39	30. Li G, Deng O, Feng J, Li F, Xiong N. He O. Clinical Characteristics of Diabetic Patients with
59 60	40	COVID-19. I Diabetes Res 2020:2020:1652403 https://doi.org/10.1155/2020/1652403
00	. •	

Page 23 of 49

1 2

BMJ Open

3	1	31 Izcovich A Ragusa MA Tortosa F et al Prognostic factors for severity and mortality in patients
4	2	infacted with COVID 10: A systematic review. PLoS One 2020: 15: 002/1055
5	2	Infected with COVID-19. A systematic review. I Los One 2020, 15. e0241955.
6	2	
7	3	32. Carlou B, Hadjadj S, Wargny M, Pichelin M, Al-Salamen A, Allix I, et al. Phenotypic
8	4	characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study.
9	5	Diabetologia 2020;63:1500–15. <u>https://doi.org/10.1007/s00125-020-05180-x</u> .
10		
11	6	33. Zhu L, She Z-G, Cheng X, et al. Association of Blood Glucose Control and Outcomes in Patients
12	7	with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab 2020; 31: 1068-1077.e3.
13		0.71
14	8	34. Elamari S, Motaib I, Zbiri S, et al. Characteristics and outcomes of diabetic patients infected by
15	9	the SARS-CoV-2 Pan Afr Med I: 37 Epub ahead of print 2020 DOI: 10 11604/pami 2020 37 32 25192
16	-	
17	10	35 Yan Y Yang Y Wang F <i>et al.</i> Clinical characteristics and outcomes of patients with severe covid-
18	11	10 with diabates BMI Open Diabates Res Care 2020: 8: e001242
19	11	19 with diabetes. Divij Open Diabetes Res Care 2020, 6. e001545.
20	12	26 Lagrang Cours D. Literarg Diag A. Talawarg D. et al. II. (based as artality risk as a dal for
21	12	36. Laguna-Goya K, Utrero-Kico A, Talayero P, <i>et ul.</i> 1L-6–based mortality risk model for
22	13	hospitalized patients with COVID-19. J Allergy Clin Immunol 2020; 146: 799-807.e9.
23	14	
24	14	37. Working group for the surveillance and control of COVID-19 in Spain. Redondo-Bravo L, <i>et al.</i>
25	15	The first wave of the COVID-19 pandemic in Spain: characterisation of cases and risk factors for
20	16	severe outcomes, as at 27 April 2020. Eurosurveillance 2020;25:2001431. doi:10.2807/1560-
27	17	7917.ES.2020.25.50.2001431
20		
30	18	38. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: A
31	19	systematic review and meta-analysis. J Med Virol 2020; 92: 1875–1883.
32		
33	20	39. Carlson N, Nelveg-Kristensen K -E., Freese Ballegaard E, et al. Increased vulnerability to
34	21	COVID-19 in chronic kidney disease. I Intern Med 2021: joim.13239.
35		
36	22	40. Portolés I. Marques M. López-Sánchez P. <i>et al.</i> Chronic kidney disease and acute kidney injury
37	$\frac{1}{23}$	in the COVID-19 Spanish outbreak. Nephrol Dial Transplant 2020: 35: 1353–1361
38	23	in the COVID 17 optimist outbreak. Reprior Dial Transplait 2020, 00. 1000 1001.
39	24	41 Leon-Abarca IA Memon RS Rehan B et al. The impact of COVID-19 in diabetic kidney disease
40	25	and chronic kidney diseases: A nonulation based study moderily. Enub abaad of print 2020 DOI:
41	25	https://doi.org/10.1101/2020.00.12.20102025
42	20	1000000000000000000000000000000000000
43	27	40 Alabara J.D. Al Charman i A.A. Dana Illi A. at al Eastine Pland Charman d COVID 10 Constitu
44	27	42. Alanmad B, Al-Shammari AA, bennakni A, <i>et ul.</i> Fasting blood Glucose and COVID-19 Severity:
45	28	Nonlinearity Matters. Diabetes Care 2020; 43: 3113–3116.
46	20	
4/	29	43 . Lazarus G, Audrey J, Wangsaputra VK, <i>et al.</i> High admission blood glucose independently
48	30	predicts poor prognosis in COVID-19 patients: A systematic review and dose-response meta-
49 50	31	analysis. <i>Diabetes Res Clin Pract</i> 2021; 171: 108561.
50		
51	32	44. Chen L, Sun W, Liu Y, et al. Association of Early-Phase In-Hospital Glycemic Fluctuation With
52	33	Mortality in Adult Patients With Coronavirus Disease 2019. Diabetes Care 2021; dc200780.
54		
55	34	45. Kapoor R, Timsina LR, Gupta N, et al. Maintaining Blood Glucose Levels in Range (70–150
56	35	mg/dL) is Difficult in COVID-19 Compared to Non-COVID-19 ICU Patients – A Retrospective
57	36	Analysis. J Clin Med 2020; 9: 3635.
58		
59		
60		

- 46. Shen Y, Fan X, Zhang L, et al. Thresholds of Glycemia and the Outcomes of COVID-19
- Complicated With Diabetes: A Retrospective Exploratory Study Using Continuous Glucose
 - Monitoring. Diabetes Care 2021; dc201448. For peer teriew only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	Overall			
Characteristic	study	Diabetes	No diabetes	n-valu
Characteristic	population	N=448	N=1621	p-valu
	N=2069			
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,	72.0 (64.0;	67.0 (55.0;	<0.001
rige, incutait (125, 175), years	80.0)	80.0)	79.0)	<0.001
Sex (male), n (%)	1205 (60.3)	304 (67.9)	950 (58.6)	< 0.001
Glucose, mean, (SD)				
mg/dL	124 (47.7)	168 (74.4)	112 (24.8)	< 0.001
mmol/L	6.8(2.6)	9.3 (4.1)	6.2 (1.4)	
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

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

e, respectively; SD, s; i · p

Figure legend/caption

3	1	
4	2	Figure 1. Flowchart diagram
5	3	0 0
7	4	Figure 2. Proportion of events (%) during hospitalization according to the presence of diabetes.
, 8	5	
9	6	Legend: ARDS, acute respiratory distress syndrome: DM, diabetes mellitus: ICU, intensive care
10	7	unit: IMV, invasive mechanical ventilation $** p<0.001$: $** p<0.01$: $* p<0.05$
11	8	
12	Ũ	
13 14	9	Figure 3. Clinical and demographic variables associated with increased risk of in-hospital death and
15	10	the composite outcome of death or invasive mechanical ventilation.
16 17		
17	11	Legend: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD,
19 20	12	cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical
21	13	ventilation
22		
23 24	14	Figure 4. Clinical and demographic variables associated with increased risk of in-hospital death and
25	1.7	
26	15	the composite outcome of death and/or invasive mechanical ventilation in subjects with diabetes
27	16	(A) and without diabetes (B).
28		
29 30	17	Legend: CKD, chronic kidney disease: COPD, chronic obstructive pulmonary disease: CVD,
31	10	
32	18	cardiovascular disease; DM, diabetes mellitus; HF, heart failure; IMV, invasive mechanical
33 34	19	ventilation
35		
36	20	Figure 5. Spline plot demonstrating a marked non-linearity in the relationship between plasma
37	21	glucose (mg/dL) levels on admission and the log odds of death (A) and death or invasive
38	22	mechanical ventilation (IMV) rate (B). Tick marks above the horizontal axis indicate the values at
39	23	which the observations were made. The dotted lines represent the 95% confidence interval. The
40	24	model was adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD,
41	25	and COPD.
42	•	
43	26	Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure;
45	27	CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease
46		
47	28	Figure 6. Predicted probability of in-hospital death (A) and death or IMV (B) based on generalized
48	29	smoothing splines. The shaded area represents the 95% confidence interval. The model was
49	30	adjusted for age, sex, obesity, hypertension, hyperlipidaemia, history of CVD, HF, CKD, and COPD
50 51	31	
57	32	Legend: IMV, intensive mechanical ventilation; CVD, cardiovascular disease; HF, heart failure;
53	33	CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease
54	34	
55	35	
56	37	
57	38	
58	39	
59	40 41	
60	11	

1		
2		
5 4	l	
5	2	Supplement figure legend/caption
6	3	
7	4	Supplementary Figure 1 . Proportion of events (%) during hospitalization according to the presence
8	5	of diabetes and age group (A) and sex (B).
9 10	6	
10	7	Legend: ARDS, acute respiratory distress syndrome; DM, diabetes mellitus; ICU, intensive care
12	8	unit; IMV, invasive mechanical ventilation. *** p<0.001; ** p<0.01; * p<0.05
13	9	
14	10	
15 16	11	
17 19	10	
10 19	12	
20		
21		
22		
23		
24		
25 26		
27		
28		
29		
30		
31 22		
32		
34		
35		
36		
37		
38 30		
40		
41		
42		
43		
44 15		
45 46		
47		
48		
49		
50		
51 52		
53		
54		
55		
56		
5/ 50		
50 59		
60		

EXCLUSION WITHOUT COVID19 CONFIRMATION N=198 AGE YOUNGER THAN 18 N=5

GROUP WITHOUT DIABETES N=1,824

GROUP WITHOUT DIABETES N=1,621

Covid Data Save Lives N=2,306

Figure 1. Flowchart diagram

255x154mm (96 x 96 DPI)

GROUP WITH DIABETES N=482

GROUP WITH DIABETES N=448



EXCLUSION WITHOUT COVID19 CONFIRMATION N=34 AGE YOUNGER THAN 18 N=0





BMJ Open

1









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 crosssectional "Covid Data Save Lives" database study

Emilio Ortega ^{1,2,3}, Rosa Corcoy ^{4,5,6}, Mònica Gratacòs¹, Xavier Cos-Claramunt ^{1,7}, Manel Mata-Cases ^{1,8,10}, Ramon Puig- Treserra¹, 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*}

TABLE OF CONTENTS		
		PAGE
Supplementary Table 1	Basal vital signs and laboratory measurements of patients admitted for coronavirus according to the presence of diabetes mellitus	2
Supplementary Figure 1.	Proportion of events (%) during hospitalization according to the presence of diabetes and age group (A) and sex (B).	4
Supplementary Table 2.	Number of events in patients with pre-existing diabetes and stress hyperglycaemia/unknown diabetes.	5
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.	6
Supplementary Table 4.	Mortality model evaluating diabetes and interactions with other clinical comorbid conditions regarding the outcome of death.	7
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).	8
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).	9
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.	10
Supplementary text	Database description.	11

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 m ²	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		C	
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), x10 ³ /µL	8.91 (6.52)	7.47 (4.17)	< 0.001
Platelets, mean (SD), x10 ³ /µL	247 (112)	250 (116)	0.705

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			
CO2 pressure, mean (SD), mmHg	37.8 (9.95)	35.8 (7.42)	0.007
O2 pressure , mean (SD), mmHg	73.4 (35.4)	67.5 (30.9)	0.216
O2 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.



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

BMJ Open

Kor -	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%)

 BMJ Open

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

		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

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

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							

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
2/ 20
28
29
30 31
37
32 33
34
35
36
37
38
39
40
41
42
43
44
45

1 2

> 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		O_{h}	0.190	
p<0.05 ** p<0.01 *** p<0.001						

BMJ Open

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
12
10
20
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46

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			nvasive mechanical v	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				N		

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

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

BMJ Open

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					reporteu		
	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							
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml							

5 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7 Lines:4-11
Tonow up, and data concetion	
 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.Page 7 Lines:19-24 Page 8 Lines:1-4RECORD 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
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.
	of participants. Describe methods of follow-up <i>Case-control study</i> - 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 <i>Cross-sectional study</i> - 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 <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case7Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

Page 48 o	f 49
-----------	------

Data sources/	8	For each variable of interest,			Page 7
measurement		give sources of data and details			Lines:12-16
		of methods of assessment			
		(measurement).			
		Describe comparability of			
		assessment methods if there is			
		more than one group			
Bias	9	Describe any efforts to address			Page 9
		potential sources of bias			Lines:1-7
Study size	10	Explain how the study size was			NA
•		arrived at			
Quantitative	11	Explain how quantitative			Page 8
variables		variables were handled in the			Lines:21-24
		analyses. If applicable, describe			
		which groupings were chosen,			
		and why			
Statistical	12	(a) Describe all statistical	N/A		Page 8
methods		methods, including those used to	1 6		Lines:21-24
		control for confounding			Page 9
		(b) Describe any methods used			Lines: 1-12
		to examine subgroups and			
		interactions			
		(c) Explain how missing data		И.	
		were addressed			
		(d) <i>Cohort study</i> - 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 49 of 49

		analyses			
Data access and				RECORD 12.1: Authors should	Page 7
cleaning methods				describe the extent to which the	Lines:12-18
				investigators had access to the database	
				population used to create the study	
				population.	
				RECORD 12.2: Authors should	
				provide information on the data	
		$\mathbf{\wedge}$		cleaning methods used in the study.	
Linkage				RECORD 12.3: State whether the	NA
-				study included person-level,	
				institutional-level, or other data linkage	
		· · ·		across two or more databases. The	
				methods of linkage and methods of	
			0	linkage quality evaluation should be	
				provided.	
Results					
Participants	13	(a) Report the numbers of		RECORD 13.1: Describe in detail the	Page 9
		individuals at each stage of the		selection of the persons included in the	Lines:18-24
		study (<i>e.g.</i> , numbers potentially		study (<i>i.e.</i> , study population selection)	
		eligible, examined for eligibility,		including filtering based on data	
		confirmed eligible, included in		quality, data availability and linkage.	
		the study, completing follow-up,		The selection of included persons can	
		and analysed)		be described in the text and/or by	
		(b) Give reasons for non-		means of the study flow diagram.	
		(a) Consider use of a flow			
		(c) Consider use of a flow			
Descriptive data	1/	(a) Give characteristics of study			Dago 10
Descriptive data	14	participants (<i>a g</i> demographic			I age 10 $I \text{ inos} \cdot 1 \cdot 11$
		clinical social) and information			Lines.1-11
		on exposures and potential			
		confounders			
		(b) Indicate the number of			
		participants with missing data			
			1	1	1
		For near review only - h	ttp://hmionen.hmi.com/sit/	e/about/quidelines.yhtml	
		for peer review only - n	step., / origoperi.orij.com/sit	c, asoad guidennes.mem	
		for each variable of interest			
----------------	----	--------------------------------------------	-----	--------------------------	--------------
		(c) Cohort study - summarise			
		follow-up time (<i>e.g.</i> , average and			
		total amount)			
Outcome data	15	<i>Cohort study</i> - Report numbers			Page 10
		of outcome events or summary			Lines: 12-19
		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			
Main results	16	(a) Give unadjusted estimates			Page 10
		and, if applicable, confounder-			Lines:20-25
		adjusted estimates and their	N h		Page 11
		precision (e.g., 95% confidence			Lines: 1-23
		interval). Make clear which			Page 12
		confounders were adjusted for			Lines:1-4
		and why they were included			
		(b) Report category boundaries			
		when continuous variables were		1	
		categorized			
		(c) If relevant, consider			
		translating estimates of relative			
		risk into absolute risk for a			
		meaningful time period			
Other analyses	17	Report other analyses done—			Page 12
		e.g., analyses of subgroups and			Lines5-17
		interactions, and sensitivity			
		analyses			
Discussion					
Key results	18	Summarise key results with			Page 12
		reference to study objectives			Lines: 19-24
Limitations	19	Discuss limitations of the study,		RECORD 19.1: Discuss the	Page 14

		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	2/ 1		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		4	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.

*Checklist is protected under Creative Commons Attribution (<u>CC BY</u>) license.