Sex disparities in COVID-19 outcomes of inpatients with diabetes: insights from the CORONADO study

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Abstract

Objective: Male sex is one of the determinants of severe coronavirus diseas-e-2019 (COVID-19). We aimed to characterize sex differences in severe outcomes in adults with diabetes hospitalized for COVID-19.
Methods: We performed a sex-stratified analysis of clinical and biological features and outcomes (i.e. invasive mechanical ventilation (IMV), death, intensive care unit (ICU) admission and home discharge at day 7 (D7) or day 28 (D28)) in 2380 patients with diabetes hospitalized for COVID-19 and included in the nationwide CORONADO observational study (NCT04324736).
Results: The study population was predominantly male (63.5%). After multiple adjustments, female sex was negatively associated with the primary outcome (IMV and/or death, OR: 0.66 (0.49–0.88)), death (OR: 0.49 (0.30–0.79)) and ICU admission (OR: 0.57 (0.43–0.77)) at D7 but only with ICU admission (OR: 0.58 (0.43–0.77)) at D28. Older age and a history of microvascular complications were predictors of death at D28 in both sexes, while chronic obstructive pulmonary disease (COPD) was predictive of death in women only. At admission, C-reactive protein (CRP), aspartate amino transferase (AST) and estimated glomerular filtration rate (eGFR), according to the CKD-EPI formula predicted death in both sexes. Lymphocytopenia was an independent predictor of death in women only, while thrombocytopenia and elevated plasma glucose concentration were predictors of death in men only.
Conclusions: In patients with diabetes admitted for COVID-19, female sex was associated with lower incidence of early severe outcomes, but did not influence the overall in-hospital mortality, suggesting that diabetes mitigates the female protection from COVID-19 severity. Sex-associated biological determinants may be useful to optimize COVID-19 prevention and management in women and men.

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Introduction

Older age and specific comorbidities, such as diabetes, have been identified as the main factors associated with severe forms of coronavirus disease-2019 (COVID-19) (1, 2). Male sex was also recognized as a determinant of poor prognosis, and the characterization of sex differences in COVID-19 clinical presentation and outcomes could thus provide important insights to optimize prevention and management of the disease in women and men (3).

Sex differences in the course of infectious diseases and immune responses have already been described (4). As reported in previous coronavirus outbreaks (5, 6), sex-stratified analyses of people affected by COVID-19 in China, Europe and the United States showed a clear male predominance in hospitalization rate and intensive care unit (ICU) admission and death, while the infection rates seem to be equal between men and women (7, 8). For instance, 41.9% of the 1099 patients hospitalized for COVID-19 were women in one of the first Chinese reports (9), and similar trends were observed in different regions of the world as summarized by the Global Health 50/50 (10). Such a male predominance was also observed regarding ICU admissions and the use of invasive mechanical ventilation (IMV). Accordingly, in large series of patients admitted to ICU in Italy (n= 1591) and in the United Kingdom (n= 10 917), men accounted for 82 and 70% of the whole population, respectively (11, 12). In a case series including 463 patients hospitalized for COVID-19 in Detroit (USA), male sex was similarly associated with over two-fold

increased odds of ICU admission, IMV or mortality (13). In the analysis of the OpenSAFELY platform in the United Kingdom, identifying 10 926 COVID-19-related deaths from primary care records of 17 278 392 adults, mortality was independently associated with male sex (HR = 1.59 (1.53–1.65)) (14).

In a recent analysis of 319 349 people with diabetes from the total Scottish population, male sex was also associated with a higher risk of severe COVID-19 outcome, combining death and admission to critical care unit (15). In contrast, observations from the UK Biobank suggest that diabetes similarly increased the risk of COVID-19-related mortality in women and men (16). Nevertheless, to date, sex differences in COVID-19 presentation and outcomes have been scarcely investigated in patients with diabetes. In the present sex-stratified analysis, we compared the clinical and biological features and outcomes in women and men included in the CORONADO (CORONAvirus SARS-CoV-2 and Diabetes Outcomes) study, a nationwide observational study dedicated to patients with diabetes hospitalized for COVID-19. We identified sex-specific clinical and biological determinants of in-hospital COVID-19-related mortality.

Methods

Study design and population

The French multicenter nationwide CORONADO study (ClinicalTrials.gov NCT04324736) is a retrospective and prospective study designed to describe the phenotypic characteristics and outcomes of patients with diabetes admitted to hospital for COVID-19 between March 10 and April 10, 2020. The study was conducted in accordance with the declaration of Helsinki and French legislation and obtained approvals from the local ethics committee (IRB/IEC – GNEDS; Ref.CORONADOV2), the CEREES (n° INDS:1544730) and the CNIL (DR-2020-155/920129).

Full study details have been reported previously (17). Inclusion criteria were (i) hospitalization in a dedicated COVID-19 unit for biologically (SARS-CoV-2 PCR) and/or clinically/radiologically attested COVID-19 (i.e. ground-glass opacity and/or crazy paving on chest CT scan); (ii) personal history of diabetes or newly diagnosed diabetes on admission (i.e. $HbA_{1c} \geq 6.5\%$ during the 7 days following the hospitalization).

Participants with available data for sex, age, BMI and main outcomes were considered for analysis. Focusing on the relationship between sex and COVID-19 outcomes, the present analysis excluded patients receiving treatment interfering with sex hormone metabolism or action and patients without information on their routine treatment (see flow chart, Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

This article follows the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guidelines for cohort studies.

Data collection

The procedure and details of data collection have been previously described (17). Briefly, classification and duration of diabetes, body weight and height (and/or BMI value) were collected as noted in the medical file by the physician in charge of the patient. HbA_{1c} considered in the analysis was determined locally in the 7 days following admission or, if not available, was the result of the last routine determination in the previous 6 months. Diabetic microvascular and macrovascular complications, as well as comorbidities and routine treatment, were noted as reported in the medical file. Whenever needed, clinical research associates and/or physicians of participating centers were asked to contact the patient's general and/or specialist practitioners, regular pharmacists and/or biomedical laboratory to complete the data collection. Moreover, COVID-19-related clinical, radiological and biological characteristics on admission were collected as well as the clinical evolution during hospital stays.

Outcomes

The pre-specified primary composite endpoint combined IMV and/or death at day 7 (D7). Patients discharged before D7 were systematically contacted on D7 to check for the non-occurrence of these events. Pre-specified secondary outcomes included death, IMV, ICU admission and hospital discharge, all considered at D7 and day 28 (D28) for all patients alive and not discharged at D7.

Statistical analysis

In this *post-hoc* analysis, the CORONADO study population was described according to the sex of the participants. Quantitative variables were expressed as mean ± S.D. or median (25th–75th percentile), and categorical variables as the number (%) of patients. Logistic regressions were conducted to test the association of each variable with sex, without adjustment and adjusted for age. In these models, the natural-log transformation was systematically considered to better fulfill the linearity assumption, and

finally applied to BMI, diabetes duration and biological variables. The quantitative variables were also standardized. The same approach was also performed to study the association with the different outcomes at D7 and D28, separately in men and women. Multiple logistic regression analyses were performed by sex. Models were adjusted for age, BMI, smoking, hypertension, microvascular complications, macrovascular complications, chronic obstructive pulmonary disease (COPD) and treated obstructive sleep apnea (OSA). Finally, a sensitivity analysis of sex-associated predictive factors of COVID-19-related death at D28 was performed. Four therapeutic classes have been introduced into this exploratory model, in addition to the variables selected in the previous models: metformin, insulin, DDP4-inhibitors and statins.

All statistical tests were two-sided with a type 1 error set at 5%. All analyses were performed on available data, without imputation, using statistical software R version 4.0.3 (https://cran.r-project.org).

Results

Sex-associated characteristics of patients prior to admission

The present analysis included 2380 patients with diabetes and confirmed diagnosis of COVID-19 admitted in 68 French hospitals between March 10 and April 10, 2020. Of note, 88 patients were excluded due to routine treatments interfering with sex hormone metabolism or action (see flow chart, Supplementary Fig. 1). A male predominance was observed in the population which included 1512 men (63.5%) and 868 women (36.5%). Their clinical characteristics before admission (i.e. medical history and routine treatment) are detailed in Table 1 and Supplementary Table 1. Women were older than men (median age of 71 (61–81) vs 69 (60–78) years), with almost one-third of them aged 80 years or more. Women were also characterized by a higher median BMI (29.8 (25.7–34.5) vs 27.8 (24.9–31.2) kg/m^2) and a higher prevalence of obesity (49.2% vs 33.2%) than men. Type 2 diabetes (T2D) was the most common type of diabetes in both sexes (87.3% in women and 87.8% in men), and no difference was observed between women and men in terms of diabetes duration or HbA_{1c} level. Current or former smokers were more frequently men (53.8%) than women (13.8%). Macrovascular complications were less frequent in women (31.3% vs 43.0%) than in men, while the prevalence of microvascular complications was similar in both sexes. More details on diabetes complications are provided in Supplementary Table 1. Dyslipidemia and COPD were also more prevalent in men than in women, but no sex difference was observed for hypertension, heart failure and OSA (Table 1). Considering medications before admission, men were more frequently treated with metformin, diuretics, antiplatelet agents and statins than women, while no difference was observed with other glucose-lowering or cardiovascular drugs (Supplementary Table 1).

Sex differences in COVID-19 features at admission

Clinical symptoms as well as radiological and biological findings at admission are detailed in Table 2. Almost all patients were symptomatic without any influence of sex on the median duration of symptoms (5 (2–9) days). Men had a fever more frequently than women (77.9% vs 72.4%), while women exhibited digestive symptoms more frequently than men (39.3% vs 32.0%), even after age adjustment. No difference was observed in terms of respiratory status at admission, with similar frequencies of dyspnea and oxygen therapy requirement observed in women and men. Plasma glucose and estimated glomerular filtration rate, according to the CKD-EPI formula (eGFR) were similar in both sexes, but men exhibited an exacerbated inflammatory response compared to women, with higher plasma levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH), as well as lower lymphocyte and platelet counts than women.

Influence of sex on COVID-19 outcomes

The incidence of COVID-19 outcomes in women and men at D7 and D28 is shown in Table 3. In univariate analysis, female sex was inversely associated with the primary composite outcome (IMV and/or death), IMV and ICU admission at both time points, and was positively associated with home discharge at D28. Of note, the median length of stay before discharge, analyzed at D28, was similar in both sexes (10.4 ± 6.1 days in women vs 10.5 ± 6.4 days in men). After multiple adjustments for confounding factors, female sex was negatively associated with the primary composite outcome (OR 0.66 (0.49–0.88)), death (OR 0.49 (0.30–0.79)) and ICU admission (OR 0.57 (0.43-0.77)) at D7. At D28, only ICU admission (OR 0.58 (0.43–0.77)) remained significantly associated with female sex in the multivariable model.

Obesity has been associated with an increased risk of severe outcomes in people hospitalized for COVID-19, including those with T2D (17, 18). Therefore, we analyzed

Table 1 Clinical characteristics of coronavirus SARS-CoV-2 and diabetes outcomes (CORONADO) participants prior to admission according to sex. Data are presented as *n* (%) or median (25th; 75th percentile). Associated *P*-values are given using Wald tests (logistic regression model not adjusted and adjusted for age).

Clinical features	All	Women	Men	*P*-value	Age-adjusted *P*-value
Total, *n*	2380	868	1512		
Age (years)	70 (61; 79)	71 (61; 81)	69 (60; 78)	**0.001**	
Age categories, *n*	2380	868	1512	**<0.001**	
<50 -years	183 (7.7%)	68 (7.8%)	115 (7.6%)		
50–59 years	349 (14.7%)	119 (13.7%)	230 (15.2%)		
60–69 years	634 (26.6%)	207 (23.8%)	427 (28.2%)		
70–79 years	655 (27.5%)	218 (25.1%)	437 (28.9%)		
>80 years	559 (23.5%)	256 (29.5%)	303 (20.0%)		
BMI (kg/m^2)	28.4 (25.1; 32.4)	29.8 (25.7; 34.5)	27.8 (24.9; 31.2)	**<0.001**	**<0.001**
BMI classes, *n*	2380	868	1512	**<0.001**	**<0.001**
<25 kg/m^2	587 (24.7%)	190 (21.9%)	397 (26.3%)		
25–29.9 kg/m^2	864 (36.3%)	251 (28.9%)	613 (40.5%)		
≥30 kg/m^2	929 (39.0%)	427 (49.2%)	502 (33.2%)		
Ethnicity, *n*	2031	740	1291	0.385	0.173
EU	1179 (58.1%)	436/ (58.9%)	743 (57.6%)		
MENA	416/ (20.5%)	138 (18.6%)	278 (21.5%)		
AC	361/ (17.8%)	140 (18.9%)	221 (17.1%)		
AS	75 (3.7%)	26 (3.5%)	49 (3.8%)		
Diabetes classification, *n*	2380	868	1512	0.472	0.220
Type 2	2086 (87.6%)	758 (87.3%)	1328 (87.8%)		
Type 1	54 (2.3%)	24 (2.8%)	30 (2.0%)		
Others	240 (10.1%)	86 (9.9%)	154 (10.2%)		
Diabetes duration (years), *n* = 1610	11 (5; 20)	12 (5; 20)	11 (5; 19)	0.235	0.299
HbA_{1c} (%), *n* = 1580	7.7 (6.8; 9.0)	7.7 (6.9; 9.0)	7.7 (6.8; 9.0)	0.618	0.873
Smoking, *n*	1994	703	1291	**<0.001**	**<0.001**
Never	1202 (60.3%)	606 (86.2%)	596 (46.2%)		
Former	674 (33.8%)	79 (11.2%)	595 (46.1%)		
Current	118/ (5.9%)	18 (2.6%)	100 (7.7%)		
Microvascular complications, *n*	1760	668	1092		
	778 (44.2%)	300 (44.9%)	478 (43.8%)	0.641	0.612
Macrovascular complications, *n*	2248	821	1427		
	870 (38.7%)	257 (31.3%)	613 (43.0%)	**<0.001**	**<0.001**
Comorbidities					
Hypertension, *n*	2360	859	1501		
	1817 (77.0%)	672 (78.2%)	1145 (76.3%)	0.279	0.854
Dyslipidemia, *n*	2320	849	1471		
	1122 (48.4%)	377 (44.4%)	745 (50.6%)	**0.004**	**0.001**
Heart failure, *n*	2268	824	1444		
	272 (12.0%)	111 (13.5%)	161 (11.1%)	0.102	0.291
COPD, *n*	2329	846	1483		
	228 (9.8%)	65 (7.7%)	163 (11.0%)	**0.01**	**0.003**
Treated OSA, *n*	2217	805	1412		
	245 (11.1%)	78 (9.7%)	167 (11.8%)	0.123	0.131

HbA_{1c} corresponds to the HbA_{1c} value determined in the first 7 days following admission or the most recent value available in the 6 months prior to admission; microvascular complications correspond to severe diabetic retinopathy, diabetic kidney disease and/or history of diabetic foot ulcer; macrovascular complications correspond to ischemic heart disease, cerebrovascular disease and/or peripheral artery disease; Ethinicity: AC, African or Caribbean; AS, Asian; EU, Europid; MENA, Middle East North Africa; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

the incidence of the primary composite outcome and its separate components at D28 in women and men according to BMI categories (<25, 25–29.9 and ≥30 kg/m^2) (Table 4). The primary composite outcome and death were not influenced by overweight or obesity status, irrespective of sex. In contrast, in the multivariable model, men with overweight (OR: 2.23 (1.37–3.63)) or obesity (OR: 2.30 (1.39–3.80)) exhibited an increased risk of IMV compared to those with BMI < 25 kg/m^2. In women, the association between obesity and IMV was no longer significant after multiple adjustments (OR: 1.51 (0.70–3.29)), suggesting that, among people with diabetes, men are more susceptible

Table 2 Clinical and biological characteristics of coronavirus SARS-CoV-2 and diabetes outcomes (CORONADO) participants at admission, according to sex. Data are presented as *n* (%) or median (25th; 75th percentile). Associated *P*-values are given using Wald tests (logistic regression model not adjusted and adjusted for age).

COVID-19-related characteristics	Available data	All	Women	Men	*P*-value	Age-adjusted *P*-value
Total, *n*		2380	868	1512		
Positive SARS-CoV-2 PCR	2306	2189/2306 (94.9%)	792/831 (95.3%)	1397/1475 (94.7%)	0.532	0.445
COVID-19 symptoms	2379	2256/2379 (94.8%)	817/867 (94.2%)	1439/1512 (95.2%)	0.320	0.494
Time between symptom onset and hospital admission (days)	2342	5 (2; 9)	5 (2; 8)	6 (3; 9)	0.066	0.206
Clinical presentation						
Fever	2348	1782/2348 (75.9%)	623/860 (72.4%)	1159/1488 (77.9%)	**0.003**	**0.008**
Fatigue	2274	1416/2274 (62.3%)	517/830 (62.3%)	899/1444 (62.3%)	0.988	0.733
Cough	2316	1549/2316 (66.9%)	557/840 (66.3%)	992/1476 (67.2%)	0.658	0.953
Cephalalgia	2205	307/2205 (13.9%)	122/810 (15.1%)	185/1395 (13.3%)	0.239	0.049
Dyspnea	2345	1509/2345 (64.3%)	538/860 (62.6%)	971/1485 (65.4%)	0.168	0.212
Oxygen therapy requirement	1840	1214/1840 (66.0%)	441/669 (65.9%)	773/1171 (66.0%)	0.968	0.892
Rhinitis and/or pharyngeal signs	2165	193/2165 (8.9%)	72/802 (9.0%)	121/1363 (8.9%)	0.937	0.679
Agueusia and/or Anosmia	2078	307/2078 (14.8%)	98/755 (13.0%)	209/1323 (15.8%)	0.082	0.211
Digestive disorders	2273	788/2273 (34.7%)	327/832 (39.3%)	461/1441 (32.0%)	**<0.001**	**<0.001**
Chest CT imaging						
Abnormal chest CT	1701	1648/1701 (96.9%)	560/580 (96.6%)	1088/1121 (97.1%)	0.571	0.617
Ground-glass opacity/crazy paving	1678	1517/1678 (90.4%)	510/572 (89.2%)	1007/1106 (91.0%)	0.214	0.288
Biological findings						
Admission plasma glucose (mg/dL)	1772	170 (127; 240)	165 (124; 234)	172 (128; 245)	0.167	0.303
eGFR (CKD-EPI) (mL/min/1.73 m^2)	2218	68.5 (41.4; 89.7)	67.3 (39.0; 90.4)	69.1 (42.9; 89.2)	0.492	0.731
ALT (% ULN)	2114	0.62 (0.42; 1.00)	0.59 (0.40; 0.96)	0.64 (0.43; 1.02)	**0.039**	0.115
AST (% ULN)	2086	1.06 (0.74; 1.59)	1.00 (0.71; 1.46)	1.10 (0.76; 1.68)	**0.008**	**0.013**
GGT (% ULN)	1980	0.95 (0.57; 1.80)	1.10 (0.63; 2.12)	0.90 (0.53; 1.62)	**<0.001**	**<0.001**
Hemoglobin (g/dL)	2323	12.7 (11.4; 14.2)	12.1 (10.9; 13.2)	13.2 (11.7; 14.6)	**<0.001**	**<0.001**
White cell count (10^3/mm^3)	2321	6500 (4970; 8800)	6400 (4900; 8585)	6600 (5000; 8800)	0.105	0.088
Lymphocyte count (10^3/mm^3)	2249	1000 (700; 1400)	1100 (740; 1548)	950 (670; 1305)	**0.001**	**<0.001**
Platelet count (10^3/µL)	2320	201 (155; 259)	217 (168; 280)	191 (149; 246)	**<0.001**	**<0.001**
CRP (mg/L)	2217	84.5 (40.2; 147.0)	66.6 (31.0; 127.0)	96.0 (47.0; 155.5)	**<0.001**	**<0.001**
LDH (IU/L)	1218	346 (263; 495)	331 (256; 444)	357 (269; 515)	**0.019**	**0.022**

ALT, alanine amino transferase; AST, aspartate amino transferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate according to the CKD-EPI formula; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 3 Clinical outcomes at day 7 (D7) and day 28 (D28) following hospital admission.

COVID-19-related outcomes	All	Women	Men	OR (95% CI)		*P*-value	
				Unadjusted	Multi adjusted	Unadjusted	Multi-adjusted
n	2380	868	1512				
At 7 days							
Primary composite outcome	688 (28.9%)	204 (23.5%)	484 (32.0%)	**0.65 (0.54–0.79)**	**0.66 (0.49–0.88)**	**<0.001**	**0.005**
Death	243 (10.2%)	79 (9.1%)	164 (10.8%)	0.82 (0.62–1.09)	**0.49 (0.30–0.79)**	0.176	**0.004**
IMV	486 (20.4%)	136 (15.7%)	350 (23.1%)	**0.62 (0.50–0.77)**	0.71 (0.50–1.01)	**<0.001**	0.053
Admission in ICU	732 (30.8%)	200 (23.0%)	532 (35.2%)	**0.55 (0.46–0.67)**	**0.57 (0.43–0.77)**	**<0.001**	**<0.001**
Home discharge	476 (20.0%)	181 (20.9%)	295 (19.5%)	1.09 (0.88–1.34)	1.03 (0.76–1.38)	0.431	0.861
At 28 days							
Primary composite outcome	844 (35.5%)	265 (30.5%)	579 (38.3%)	**0.71 (0.59–0.85)**	0.77 (0.59–1.01)	**<0.001**	0.059
Death	473 (19.9%)	156 (18.0%)	317 (21.0%)	0.83 (0.67–1.02)	0.76 (0.54–1.08)	0.078	0.129
IMV	509 (21.4%)	142 (16.4%)	367 (24.3%)	**0.61 (0.49–0.76)**	0.71 (0.51–1.00)	**<0.001**	0.053
Admission in ICU*	753 (31.7%)	207 (23.9%)	546 (36.3%)	**0.55 (0.46–0.67)**	**0.58 (0.43–0.77)**	**<0.001**	**<0.001**
Home discharge	1197 (50.3%)	463 (53.3%)	734 (48.5%)	**1.21 (1.03–1.43)**	1.14 (0.88–1.48)	**0.024**	0.312

Multi-adjusted model includes adjustment on age, BMI, smoking, microvascular complications, macrovascular complications, hypertension, COPD and treated OSA. Primary composite outcome combines IMV and/or death.
*Data available for 2372 (women: 866; men: 1506).
ICU, intensive care unit; IMV, invasive mechanical ventilation; OR, women vs men odds ratio.

than women to the worsening effect of obesity on COVID-19 respiratory failure.

Sex-dependent predictors of COVID-19 mortality at D28

We assessed predictive factors of COVID-19 death at D28 in men and women separately to determine whether some of them could be sexually dimorphic. The first multivariable model included the main patient characteristics prior to admission (Fig. 1A). After multiple adjustments, older age and a history of microvascular complications were associated with a greater risk of death in both sexes, while COPD was a predictor of death in women only. HbA_{1c} was not included in this model but age- and BMI-adjusted logistic regression analyses revealed that HbA_{1c} was not associated with COVID-19 mortality, neither in women nor in men (Supplementary Fig. 2A). A sensitivity analysis was further performed to assess the influence of routine treatments previously suspected to interfere with the COVID-19 course (metformin, insulin, DPP4-inhibitors and statins) (19), providing similar results. Of note, metformin was associated with a lower risk of death at D28 in men only, whereas insulin therapy was associated with an increased risk of death at D28 in women only (Supplementary Tables 2 and 3).

The second multivariable model included age, BMI and the main biological parameters at admission. An increase in plasma CRP and aspartate amino transferase (AST) levels, as well as a decrease in eGFR, was associated with the occurrence of death at D28 in both men and women (Fig. 1B). Notably, a decreased lymphocyte count was an independent predictor of death in women only. In contrast, a decreased platelet count and increased plasma glucose were independent predictors of death in men only. Accordingly, in age- and BMI-adjusted linear analysis, admission plasma glucose was also positively associated with death in men ($P = 0.007$) but not in women ($P = 0.184$) (Supplementary Fig. 2B).

To further investigate the sex-specific association between biomarkers at admission and death at D28, we used cut-off values previously described to correlate with increased COVID-19 severity or mortality (CRP, LDH, lymphocyte count) (20, 21) or recognized as clinically relevant (platelet count, eGFR, plasma glucose, AST) (Fig. 2). After multiple adjustments and consistent with the previous model, lymphocytopenia (<1000/mm^3) was an independent predictor of death in women only while high plasma glucose at admission (>180 mg/dL) was predictive of death in men only. Increased plasma concentrations of LDH (>365 IU/L), CRP (>41.2 mg/L) and AST (>3 ULN), as well as decreased eGFR values (CKD-EPI, <60 mL/min/1.73 m^2), were independent predictors of death at D28 in both sexes.

Discussion

The present analysis from the nationwide CORONADO study reveals sex differences in clinical and biological features of patients with diabetes hospitalized for COVID-19, as well as early predictors of COVID-19 severe outcomes.

Table 4 Association of overweight and obesity status with COVID-19-related severe outcomes at day 28 (D28) according to sex.

	Primary outcome at D28					Death at D28					IMV at D28				
	Events, *n*/ participants, *n* (%)	Unadjusted		Adjusted*		Events, *n*/ participants, *n* (%)	Unadjusted		Adjusted*		Events, *n*/ participants, *n* (%)	Unadjusted		Adjusted*	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
In men, *n* = 1512															
BMI subgroups															
<25 kg/m^2	141/397 (35.5%)	Ref		Ref		98/397 (24.7%)	Ref		Ref		60/397 (15.1%)	Ref		Ref	
25–29.9 kg/m^2	234/613 (38.2%)	1.12 (0.86–1.46)	0.393	1.22 (0.85–1.75)	0.291	121/613 (19.7%)	0.75 (0.55–1.02)	0.063	0.89 (0.57–1.40)	0.616	157/613 (25.6%)	**1.93 (1.39–2.69)**	**<0.001**	**2.23 (1.37–3.63)**	**0.001**
≥30 kg/m^2	204/502 (40.6%)	1.24 (0.95–1.63)	0.117	1.25 (0.85–1.84)	0.248	98/502 (19.5%)	0.74 (0.54–1.02)	0.063	0.75 (0.45–1.23)	0.249	150/502 (29.9%)	**2.39 (1.71–3.34)**	**<0.001**	**2.30 (1.39–3.80)**	**0.001**
P-value*	–		0.291		0.459	–		0.111		0.507	–		**<0.001**		**0.001**
In Women, *n* = 868															
BMI subgroups															
<25 kg/m^2	49/190 (25.8%)	Ref			Ref	37/190 (19.5%)	Ref		Ref		19/190 (10.0%)	Ref		Ref	
25–29.9 kg/m^2	75/251 (29.9%)	1.23 (0.80–1.87)	0.344	1.34 (0.75–2.39)	0.318	48/251 (19.1%)	0.98 (0.61–1.58)	0.926	1.08 (0.55–2.16)	0.816	35/251 (13.9%)	1.46 (0.81–2.64)	0.213	1.61 (0.70–3.70)	0.263
≥30 kg/m^2	141/427 (33.0%)	1.42 (0.97–2.08)	0.073	1.31 (0.76–2.28)	0.333	71/427 (16.6%)	0.82 (0.53–1.28	0.391	1.05 (0.54 –2.04)	0.882	88/427 (20.6%)	**2.34 (1.38–3.96)**	**0.002**	1.51 (0.70–3.29)	0.296
P value*	–		0.186		0.546	–		0.594		0.973	–		**0.002**		0.480

The primary outcome is defined as invasive mechanical ventilation (IMV) and/or death at D28. Therefore, by design, some patients met the two events, and the sum of both death and IMV is greater than the number of primary outcomes.
Ref., Reference group.

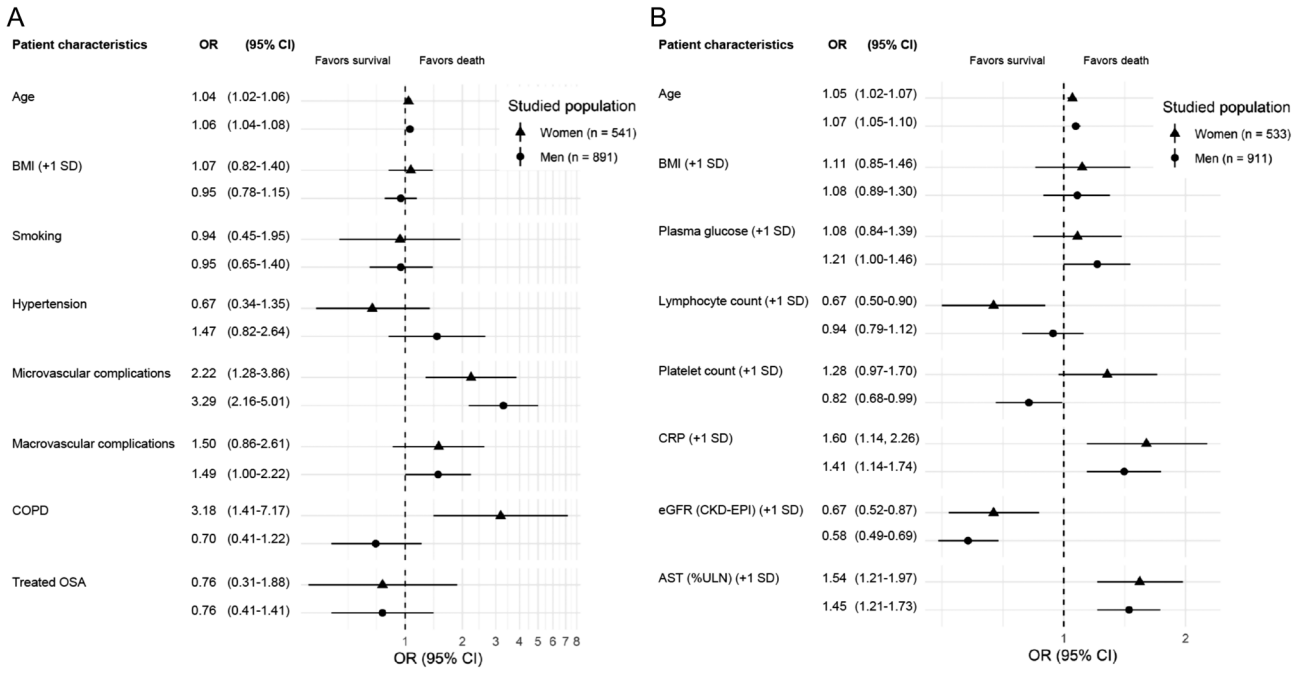

Figure 1

Sex-associated predictive factors of COVID-19-related death at day 28 (D28). Multivariable analysis of death at D28: covariates prior to (Model A) and at admission (Model B). Model A was applied to 541 women and 891 men yielding respectively 80 and 164 deaths at 28 days. Model B was applied to 533 women and 911 men yielding respectively 79 and 175 deaths at 28 days. Regarding quantitative variables: all were natural-log transformed, except for age, and the ORs correspond to an increase of 1 s.d. after standardization. Microvascular complications correspond to severe diabetic retinopathy, diabetic kidney disease and/or history of diabetic foot ulcer; macrovascular complications correspond to ischemic heart disease, cerebrovascular disease and/or peripheral artery disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; eGFR, estimated glomerular filtration rate was determined by the CKD-EPI formula; AST, aspartate amino transferase; ULN, upper limit of normal; OR, odds ratio.

Indeed, female sex was associated with a lower risk of COVID-19-related severe outcomes at D7 (i.e. primary composite outcome, death and ICU admission), while sex did not influence death at D28. In addition, we identified sex-associated determinants of death at D28, namely COPD and lymphopenia in women vs thrombocytopenia and elevated admission plasma glucose in men.

The CORONADO population was characterized by a male predominance, with men accounting for almost two-thirds of all people with diabetes hospitalized for COVID-19, as previously described regardless of diabetic status (9, 22). This is in agreement with previous reports worldwide in which male sex was associated with increased hospitalization rate, ICU admission, IMV and mortality (9, 11, 13, 14). In a recent meta-analysis including 3 111 714 COVID-19 cases, Peckham *et al.* confirmed that men are more prone to ICU admission (OR 2.84 (2.06–3.92)) and death (OR 1.39 (1.31–1.47)) compared to women (23). Data from the whole Scottish population also revealed an association between male sex and severe COVID-19 (fatal or requiring ICU admission) in people with diabetes (15).

Hospitalized women with COVID-19 were older than men, exhibited a higher prevalence of obesity and reported digestive symptoms more frequently than men, which is consistent with a recent study in hospitalized COVID-19 patients from New Orleans (24). In our population, the worse prognosis associated with the male sex was observed at D7 but was no longer statistically significant at D28, especially when considering mortality. This suggests that diabetes mitigates sex differences by increasing COVID-19 mortality in women, although we cannot exclude a lack of power to explain our results. Consistent with the first possibility, a report from the UK Biobank cohort indicates that diabetes similarly increased the risk of fatal COVID-19 in women and men (16). Moreover, in hospitalized COVID-19 patients from New Orleans, diabetes was identified as an independent predictor of in-hospital death in women only (24). Taken together, these observations suggest that diabetes

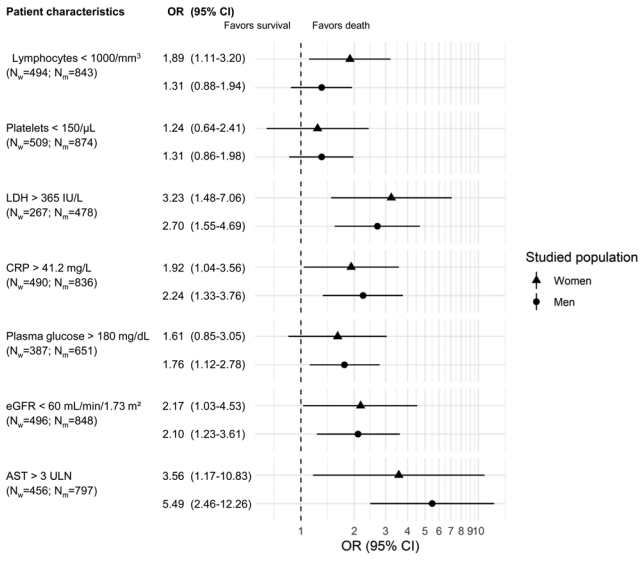

Figure 2

Association of biological markers on admission with COVID-19-related death at day 28 (D28) according to sex. Values are stratified according to cut-off values previously shown to correlate with increased disease severity or mortality in COVID-19 or clinically relevant (lymphocytes < 1000/mm^3; platelets < 150 × 10^3/µL; CRP > 41.2 mg/L; LDH > 365 IU/L; eGFR < 60 mL/min/1.73m^2; AST > 3ULN). OR, odds ratio; Nm, number of men included in the model; Nw, number of women included in the model; LDH, lactate dehydrogenase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate, according to the CKD-EPI formula; AST, aspartate amino transferase; ULN: upper limit of normal. Multi-adjustment on age, BMI, smoking, microvascular complications, macrovascular complications, hypertension, chronic obstructive pulmonary disease (COPD) and treated obstructive sleep apnea (OSA).

eliminates the female protection from severe COVID-19, at least in people who require hospital admission. Further studies including patients with and without diabetes are required to definitely establish whether diabetes blunts the relative female protection from severe COVID-19 outcomes in patients admitted to hospital.

In our population, women were older and more frequently affected by obesity. Obesity has been recognized as an independent factor for severe COVID-19 outcomes (14, 25, 26), but we found that overweight and obesity were both associated with IMV at D28 in men only. In contrast, in line with our recent findings at D7 (18), BMI status did not influence death at D28, disregarding the sex. Altogether, these observations confirm that an increased BMI promotes severe respiratory disorders rather than death, and suggest that men are more susceptible than women to the worsening effect of obesity on COVID-19 respiratory failure. Of note, women included in CORONADO were less likely than men to be former or current smokers, resulting in a lower prevalence of COPD than in men, which is consistent with previous reports (27). However, COPD was an independent predictor of death in women only. Similarly, in the New Orleans series, in which diabetes prevalence in women was over 38%, COPD was an independent predictor of ICU admission and IMV requirement in women only (24). Thus, greater attention in the detection and management of this respiratory disease in women with or without diabetes is necessary.

Among patient characteristics prior to hospitalization, the present data confirmed that older age and microvascular complications must be considered as predictive factors of death in both sexes, as recently demonstrated in the whole CORONADO population (28). At admission, inflammatory biomarkers (CRP, LDH and AST), as well as decreased eGFR, were also predictors of death at D28 in both sexes. Although women exhibited higher lymphocyte count than men at admission, a decreased lymphocyte count and lymphopenia (lymphocytes < 1000/mm^3) were predictors of death in women only. This is consistent with results reported in inpatients from New Orleans, where an elevated neutrophil-to-lymphocyte ratio was an independent predictor of death in women only (24). Since women were reported to exhibit enhanced adaptive immune responses and antibodies production to viral infections (29, 30), our observation suggests that lymphopenia may be more deleterious on COVID-19 outcomes in women than in men. In contrast, a decreased platelet count was associated with mortality in men only. Thrombocytopenia has already been described as a predictor of severe COVID-19 outcomes (31). Since men are at increased risk of venous thromboembolism (VTE) compared to women (32, 33), and coagulopathies resulting in disseminated intravascular coagulation are a major cause of COVID-19 deaths (34), thrombocytopenia could be a consequence of lethal thrombotic complications in men with diabetes (35). Accordingly, in the New Orleans series, elevated D-dimer, a marker of increased coagulation, was an independent predictor of ICU admission and death in men only (24).

Poor glycemic control during hospitalization has been already linked to severe COVID-19 outcomes in patients with diabetes (36), and fasting blood glucose was associated with mortality in individuals without known diabetes prior to hospitalization (37). However, sex stratification was not considered in these studies. Here, elevated plasma glucose level at admission, but not HbA_{1c}, was a predictor of fatal COVID-19 in men, but not in women. This is also in

agreement with recent observations (17, 38), and confirms that glucose level at admission is a stronger predictor of COVID-19 severity in patients requiring hospitalization than chronic glucose control assessed by HbA_{1c}, at least in men.

Prior-to-admission treatment with drugs previously suggested to influence COVID-19 course (metformin, insulin, DPP4-inhibitors and statins) did not modify our findings in terms of sex-associated predictive factors of death at D28. However, our results suggested that some of these therapies could alter COVID-19 outcomes differently in women and men. Thus, the reduced risk of death associated with metformin use, already reported in the whole CORONADO population (28, 39), was only observed in men. This contrasts with a recent retrospective study suggesting that metformin is associated with better survival specifically in women (40). There is thus a need for further studies to definitely characterize the sex-specific benefits of metformin in COVID-19 patients with T2D. While DPP4-inhibitors appeared to be neutral in both sexes, as reported in the whole population (41), insulin therapy was associated with higher COVID-19 mortality in women only. Apart from CORONADO, the association of previous insulin therapy with severe COVID-19 outcomes has already been reported in patients with T2D (42). Here, the association of insulin therapy with mortality in women likely reflects a more severe burden of comorbidities in women rather than a direct effect of insulin.

The underlying biological mechanisms of sex disparities in COVID-19 severity and mortality still need to be clarified. It is established that biological sex enhances immune responses to viral infections in females through the combined effects of X-linked genes and female hormones, which attenuate innate immune inflammatory response and enhance immune tolerance and antibody production (29, 30, 43). Male patients seem to exhibit higher plasma levels of innate immune cytokines, along with more robust induction of non-classical monocytes, while women develop more robust T cell activation during SARS-CoV-2 infection (44). Accordingly, in CORONADO, men exhibited higher levels of inflammatory markers than women at admission, which could explain their higher susceptibility to severe outcomes during the first week of hospitalization. Further investigations are needed to better understand the interactions between sex and diabetes in immune responses and meta-inflammation leading to severe COVID-19 (3).

To our knowledge, this is the first study to investigate sex differences in COVID-19 presentation and severe outcomes in a large population of individuals with diabetes. However, several limitations must be acknowledged. First, since the CORONADO study focused on COVID-19 inpatients with diabetes, our conclusions cannot be generalized to all COVID-19 patients with diabetes. Also, in the absence of a non-diabetic control group, we were unable to determine whether male sex differently impacts COVID-19 outcomes in people with and without diabetes, as recently suggested (16). Moreover, the observational nature of the present *post-hoc* analysis did not allow us to draw conclusions on causal relationships between comorbidities, biomarkers, routine treatments and COVID-19 outcomes. Although death at D28 appeared as the most clinically relevant and robust COVID-19 outcome, the sex stratification limited the power of statistical analyses, especially in women. Additionally, we were unable to perform analyses according to menopausal status due to the small number of women under 50 years in the CORONADO population and the very low incidence of COVID-19-related events in this subgroup. Finally, our results are hampered by missing data, especially for HbA_{1c} and other biological markers such as LDH and the lack of systematic collection of data regarding COVID-19 therapies during hospitalization.

In conclusion, in France, female sex was associated with a lower incidence of early severe outcomes including death in patients with diabetes admitted for COVID-19. However, sex did not influence the overall mortality during the hospital stay, suggesting that diabetes mitigates sex differences in COVID-19 severity. At admission, sex-associated biological determinants of COVID-19 death, namely lymphopenia in women and both hyperglycemia and thrombocytopenia in men, should be considered to optimize prevention and management strategies in women and men.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-21-0068.

Declaration of interest

M W reports grants, personal fees from Air Liquid, Allergan, Elivie, Fortil, Lifescan, NHC, Novo Nordisk, and Sanofi. M P reports grants, non-financial support or personal fees from Air Liquid, Allergan, Amgen, Elivie, Fortil, Lifescan, NHC, Novo Nordisk, and Sanofi. A A S reports personal fees from AstraZeneca and Novo Nordisk. L B non-financial support or personal fees from Abbott, Astra Zeneca, Becton Dickinson, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, and Sanofi. E C reports non-financial support or personal fees from Abbott, AlphaDiab, Air Liquide, Ascencia, Astra Zeneca, Bezins, BMS, Eli Lilly, LifeScan, Medtronic, MSD, Novartis, Novo-Nordisk, Roche Diagnostics, Sanofi, and YpsoMed. M M reports personal fees from Novo-Nordisk, Servier, and MSD. L P reports personal fees or non-financial support from, Eli Lilly, MSD, Novo Nordisk and Sanofi. J F G reports personal fees and non-financial support from Eli Lilly, personal fees and non-financial support from Novo Nordisk, personal fees and non-financial support from Gilead, and personal fees and non-financial support from AstraZeneca. S H reports grants, non-financial support or personal fees from Air Liquid, Allergan, Astra Zeneca, Bayer, Boehringer Ingelheim, Dinno Santé, Eli Lilly, Elivie, Fortil, Lifescan, LVL, Merck Sharpe

Dome, NHC, Novartis, Pierre Fabre Santé, Sanofi, Servier, and Valbiotis. B C reports grants, non-financial support or personal fees from Abbott, Allergan, Amgen, Akcea AstraZeneca, Pierre Fabre, Genfit, Gilead, Eli Lilly, Elivie, Fortil, Lifescan, Merck Sharpe Dome, NHC, Novo Nordisk, Regeneron and Sanofi. P G reports grants or personal fees from Abbott, Air Liquid, Allergan, Amgen, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Elivie, Fortil, Lifescan, Merck Sharp and Dohme, Mundipharma, NHC, Novo Nordisk, Sanofi, and Servier. The other authors report no conflict of interest.

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Guarantor's name

B C, S H and M W are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding authors (F M J and P G) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors contribution statement

B T, S S, S C, M W, J F G, B C, F M J and P G designed the study. All co-authors contributed to patient recruitment, data collection and/or data management. S C and M W performed the statistical analyses. B T, S S, S C, F M J and P G drafted the first version of the manuscript. All co-authors critically reviewed and edited the manuscript. B C, P G, S H and M P conducted the fundraising of the study. B T, S S, F M-J and P G contributed equally to this work.

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References

1 Singh AK, Gillies CL, Singh R, Singh A, Chudasama Y, Coles B, Seidu S, Zaccardi F, Davies MJ & Khunti K. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. *Diabetes, Obesity and Metabolism* 2020 **22** 1915–1924. (https://doi.org/10.1111/dom.14124)

2 Lim S, Bae JH, Kwon HS & Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nature Reviews: Endocrinology* 2021 **17** 11–30. (https://doi.org/10.1038/s41574-020-00435-4)

3 Mauvais-Jarvis F. Aging, male sex, obesity, and metabolic inflammation create the perfect storm for COVID-19. *Diabetes* 2020 **69** 1857–1863. (https://doi.org/10.2337/dbi19-0023)

4 Klein SL & Flanagan KL. Sex differences in immune responses. *Nature Reviews: Immunology* 2016 **16** 626–638. (https://doi.org/10.1038/nri.2016.90)

5 Karlberg J, Chong DSY & Lai WYY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *American Journal of Epidemiology* 2004 **159** 229–231. (https://doi.org/10.1093/aje/kwh056)

6 Alghamdi IG, Hussain II, Almalki SS, Alghamdi MS, Alghamdi MM & El-Sheemy MA. The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. *International Journal of General Medicine* 2014 **7** 417–423. (https://doi.org/10.2147/IJGM.S67061)

7 Klein SL, Dhakal S, Ursin RL, Deshpande S, Sandberg K & Mauvais-Jarvis F. Biological sex impacts COVID-19 outcomes. *PLoS Pathogens* 2020 **16** e1008570. (https://doi.org/10.1371/journal.ppat.1008570)

8 Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R & Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biology of Sex Differences* 2020 **11** 29. (https://doi.org/10.1186/s13293-020-00304-9)

9 Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC *et al.* Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine* 2020 **382** 1708–1720. (https://doi.org/10.1056/nejmoa2002032)

10 This is Gender 2021 Global Health 50/50. Available at https://globalhealth5050.org/this-is-gender-2021/

11 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020 **323** 1574–1581. (https://doi.org/10.1001/jama.2020.5394)

12 ICNARC. *Report on COVID-19 in Critical Care*, pp. 1–24. Intensive Care National Audit and Research Centre, 2020.

13 Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, Demertzis Z, Hanna Z, Failla A, Dagher C *et al.* Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. *JAMA Network Open* 2020 **3** e2012270. (https://doi.org/10.1001/jamanetworkopen.2020.12270)

14 Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020 **584** 430–436. (https://doi.org/10.1038/s41586-020-2521-4)

15 McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LAK, McAllister DA, Hutchinson S, Caparrotta TM, Mellor J, Jeyam A *et al.* Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet: Diabetes and Endocrinology* 2021 **9** 82–93. (https://doi.org/10.1016/S2213-8587(20)30405-8)

16 Jong M de, Woodward M & Peters SAE. Diabetes and COVID-19-related mortality in women and men in the UK Biobank: comparisons with influenza/pneumonia and coronary heart disease. *Diabetes Care* 2021 **44** e22–e24. (https://doi.org/10.2337/dc20-2378)

17 Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B *et al.* Phenotypic characteristics and prognosis of inpatients with COVID-19 and

diabetes: the CORONADO study. *Diabetologia* 2020 **63** 1500–1515. (https://doi.org/10.1007/s00125-020-05180-x)
18 Smati S, Tramunt B, Wargny M, Caussy C, Gaborit B, Vatier C, Vergès B, Ancelle D, Amadou C, Bachir LA *et al.* Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: results from the CORONADO study. *Diabetes, Obesity and Metabolism* 2021 **23** 391–403. (https://doi.org/10.1111/dom.14228)
19 Drucker DJ. Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. *Cell Metabolism* 2021 **33** 479–498. (https://doi.org/10.1016/j.cmet.2021.01.016)
20 Xie J, Zu Y, Alkhatib A, Pham TT, Gill F, Jang A, Radosta S, Chaaya G, Myers L, Zifodya JS *et al.* Metabolic syndrome and COVID-19 mortality among adult black patients in New Orleans. *Diabetes Care* 2020 **44** 188 - 193 . (https://doi.org/10.2337/dc20-1714)
21 Trecarichi EM, Mazzitelli M, Serapide F, Pelle MC, Tassone B, Arrighi E, Perri G, Fusco P, Scaglione V, Davoli C *et al.* Clinical characteristics and predictors of mortality associated with COVID-19 in elderly patients from a long-term care facility. *Scientific Reports* 2020 **10** 20834. (https://doi.org/10.1038/s41598-020-77641-7)
22 Zhu W, Xie K, Lu H, Xu L, Zhou S & Fang S. Initial clinical features of suspected coronavirus disease 2019 in two emergency departments outside of Hubei, China. *Journal of Medical Virology* 2020 **92** 1525–1532. (https://doi.org/10.1002/jmv.25763)
23 Peckham H, Gruijter N De, Raine C, Radziszewska A, Ciurtin C, Wedderburn L, Rosser E, Deakin C & Webb K. Male sex identified by global COVIS-19 meta-analysis as a risk factor for death and ITU admission. *Nature Communications* 2020 **11** 6317. (https://doi.org/10.21203/rs.3.rs-23651/v2)
24 Yoshida Y, Gillet SA, Brown MI, Zu Y, Wilson SM, Ahmed SJ, Tirumalasetty S, Lovre D, Krousel-Wood M, Denson JL *et al.* Clinical characteristics and outcomes in women and men hospitalized for coronavirus disease 2019 in New Orleans. *Biology of Sex Differences* 2021 **12** 20. (https://doi.org/10.1186/s13293-021-00359-2)
25 Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, Li Z, Shaw SF, Caparosa SL, Nau CL *et al.* Obesity and mortality among patients diagnosed with COVID-19: results from an Integrated Health Care Organization. *Annals of Internal Medicine* 2020 **173** 773–781. (https://doi.org/10.7326/M20-3742)
26 Caussy C, Pattou F, Wallet F, Simon C, Chalopin S, Telliam C, Mathieu D, Subtil F, Frobert E, Alligier M *et al.* Prevalence of obesity among adult inpatients with COVID-19 in France. *Lancet: Diabetes and Endocrinology* 2020 **8** 562–564. (https://doi.org/10.1016/S2213-8587(20)30160-1)
27 Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, Vries GJ De, Epperson CN, Govindan R, Klein SL *et al.* Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020 **396** 565–582. (https://doi.org/10.1016/S0140-6736(20)31561-0)
28 Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou PY, Bonnet JB, Bordier L, Bourron O, Chaumeil C *et al.* Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia* 2021 **64** 778–794. (https://doi.org/10.1007/s00125-020-05351-w)
29 Scully EP, Haverfield J, Ursin RL, Tannenbaum C & Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nature Reviews: Immunology* 2020 **20** 442–447. (https://doi.org/10.1038/s41577-020-0348-8)
30 Bunders MJ & Altfeld M. Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions. *Immunity* 2020 **53** 487–495. (https://doi.org/10.1016/j.immuni.2020.08.003)
31 Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y & Shang Y. Thrombocytopenia and its association with mortality in patients with COVID-19. *Journal of Thrombosis and Haemostasis* 2020 **18** 1469–1472. (https://doi.org/10.1111/jth.14848)
32 Baglin T, Luddington R, Brown K & Baglin C. High risk of recurrent venous thromboembolism in men. *Journal of Thrombosis and Haemostasis* 2004 **2** 2152–2155. (https://doi.org/10.1111/j.1538-7836.2004.01050.x)
33 Eichinger S, Heinze G, Jandeck LM & Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* 2010 **121** 1630–1636. (https://doi.org/10.1161/CIRCULATIONAHA.109.925214)
34 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020 **395** 1054–1062. (https://doi.org/10.1016/S0140-6736(20)30566-3)
35 Tang N, Li D, Wang X & Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis* 2020 **18** 844–847. (https://doi.org/10.1111/jth.14768)
36 Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W *et al.* Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing Type 2 diabetes. *Cell Metabolism* 2020 **31** 1068.e3–1077.e3. (https://doi.org/10.1016/j.cmet.2020.04.021)
37 Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, Xu J, Wu F, Duan L, Yin Z *et al.* Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia* 2020 **63** 2102–2111. (https://doi.org/10.1007/s00125-020-05209-1)
38 Agarwal S, Schechter C, Southern W, Crandall JP & Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalizedpatients withdiabetes and coronavirus disease 2019. *Diabetes Care* 2020 **43** 2339–2344. (https://doi.org/10.2337/dc20-1543)
39 Lalau JD, Al-Salameh A, Hadjadj S, Goronflot T, Wiernsperger N, Pichelin M, Allix I, Amadou C, Bourron O, Duriez T *et al.* Metformin use is associated with a reduced risk of mortality in patients with diabetes hospitalised for COVID-19. *Diabetes and Metabolism* 2020 **47** 101216. (https://doi.org/10.1016/j.diabet.2020.101216)
40 Bramante CT, Ingraham NE, Murray TA, Marmor S, Hovertsen S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N *et al.* Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. *medRxiv 2020.* (https://doi.org/10.1101/2020.06.19.20135095)
41 Roussel R, Darmon P, Pichelin M, Goronflot T, Abouleka Y, Ait Bachir L, Allix I, Ancelle D, Barraud S, Bordier L *et al.* Use of dipeptidyl peptidase-4 inhibitors and prognosis of COVID-19 in hospitalized patients with type 2 diabetes: a propensity score analysis from the CORONADO study. *Diabetes, Obesity and Metabolism* 2021 **23** 1162–1172. (https://doi.org/10.1111/dom.14324)
42 Yu B, Li C, Sun Y & Wang DW. Insulin treatment is associated with increased mortality in patients with COVID-19 and Type 2 diabetes. *Cell Metabolism* 2021 **33** 65–77.e2. (https://doi.org/10.1016/j.cmet.2020.11.014)
43 Mauvais-Jarvis F, Klein SL & Levin ER. Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinology* 2020 **161** bqaa127. (https://doi.org/10.1210/endocr/bqaa127)
44 Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, Silva J, Mao T, Oh JE, Tokuyama M *et al.* Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020 **588** 315–320. (https://doi.org/10.1038/s41586-020-2700-3)

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