Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research letters

Patients with diabetes are at higher risk for severe illness from COVID-19

The World Health Organisation recently declared the outbreak of severe acute respiratory syndrome Coronavirus 2 disease (COVID-19) a global pandemic [1]. It is known that people with diabetes have a higher overall risk of infection resulting from multiple perturbations of innate immunity [2]. Presently, it remains uncertain whether people with diabetes are also at higher risk of infection and, especially, at greater severity of illness associated with COVID-19. A recent meta-analysis of 30 observational studies (most of which were preprint studies that have yet to be reviewed) showed that pre-existing diabetes is significantly associated with poorer in-hospital clinical outcomes [3], but none of the included studies have examined whether the impact of diabetes on COVID-19 severity is independent of age, sex and metabolic comorbidities, such as obesity and hypertension. Therefore, in this retrospective study, we aimed to examine the association between diabetes and severity of COVID-19 illness (irrespective of metabolic comorbidities) among in-patients with confirmed COVID-19.

We retrospectively studied a cohort of 339 patients with COVID-19, who were consecutively hospitalised at four sites in Wenzhou, Zhejiang Province (China) between January and February 2020. COVID-19 was diagnosed as a positive result by high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction assay of oropharyngeal swab specimens. Clinical and laboratory data were collected in all patients at hospital admission. The severity of COVID-19 was assessed during hospitalisation and classified as mild, moderate, severe or critical, according to the COVID-19 management guidance [4]. For the purposes of this analysis, we defined mild and moderate subtypes as "non-severe COVID-19", and severe and critically ill subtypes as "severe COVID-19". Presence of diabetes was diagnosed as self-reported history of disease, a "random" plasma glucose level $\geq$ 11.1 mmol/L ($\geq$200 mg/dL) and/or a haemoglobin A1c level $\geq$ 48 mmol/mol (HbA1c $\geq$6.5%), according to widely accepted diagnostic criteria. Fasting glucose measurements were not available in most of these infected patients. The study protocol was approved by the local ethics committees of the four hospitals. Informed consent was waived by the ethics committee due to both the emergent nature of COVID-19 and the anonymised retrospective nature of the analysis.

In our cohort of 339 patients with laboratory-confirmed COVID-19, 130 (38.4%) patients had obesity (defined as body mass index $\geq$25 kg/m^2), 79 (23.3%) patients had established hypertension (defined as blood pressure $\geq$ 140/90 mmHg or specific drug treatment) and 59 (17.4%) patients had diabetes. As shown in Table 1, patients with diabetes were more likely to be older, obese and hypertensive and had higher circulating values of neutrophil count, D-dimer, liver enzymes, as well as lower lymphocyte counts, and lower albumin and HDL-cholesterol levels compared with their counterparts without diabetes. As expected, they also had higher levels of random plasma glucose at admission and haemoglobin A1c (available only in a subset of patients). Notably, patients with diabetes had a remarkably greater severity of COVID-19 illness than their counterparts without diabetes.

When we explored the association between random plasma glucose levels and severity of COVID-19 illness (stratified also by history of diabetes), we found that the proportion of severe COVID-19 illness increased progressively ($P < 0.0001$ by the Fisher's exact test) in relation to glucose abnormalities at admission: 7.1% in patients with random plasma glucose < 5.6 mmol/L (n = 127; mean $\pm$ SD: 4.95 $\pm$ 0.4 mmol/L), 20.3% in those with random plasma glucose 5.6–11 mmol/L (n = 153; mean $\pm$ SD: 7.03 $\pm$ 1.3 mmol/L), 25.6% in those with previously known diabetes (n = 39; mean $\pm$ SD: 9.32 $\pm$ 5.1 mmol/L), and 65.0% in those with random plasma glucose $\geq$ 11.1 mmol/L at hospital admission (n = 20; mean $\pm$ SD: 12.0 $\pm$ 3.7 mmol/L), respectively.

In binary logistic regression analysis, the presence of diabetes was associated with an approximate 4-fold increased risk of severe COVID-19 illness (unadjusted-odds ratio [OR] 3.83, 95% CI 2.06–7.13, $P < 0.0001$). Notably, this association remained significant even after adjustment for age, sex, obesity, hypertension and smoking history (adjusted-OR 2.05, 95% CI 1.01–4.19, $P < 0.05$). In this regression model, other variables that were independently associated with higher risk of severe COVID-19 illness were older age (adjusted-OR 1.05, 95% CI 1.02–1.08), male sex (adjusted-OR 2.01, 95% CI 1.05–4.0) and obesity (adjusted-OR 2.51, 95% CI 1.3–4.7).

Interestingly, during the revision process of this manuscript, a retrospective multicentre study has been published from a cohort of nearly 7300 confirmed cases of COVID-19 enrolled among 19 hospitals in Wuhan, Hubei Province (China) [5]. This retrospective study confirmed that pre-existing diabetes (present in 952 of these patients) was significantly associated with adverse clinical outcomes, and that diabetic patients with better controlled blood glucose (defined as glycaemic variability between 3.9 to 10 mmol/L) had a lower mortality rate than those with poorly controlled blood glucose (glycaemic variability > 10 mmol/L) during hospitalisation [5].

To date, the mechanisms underpinning the association between diabetes and risk of severe COVID-19 illness are poorly understood. It is conceivable that diabetes-induced abnormalities, such as the underlying metabolic changes, low-grade systemic inflammation and impaired innate cell-mediated immunity, may predispose these patients to infectious events of greater severity [2]. Moreover, patients with diabetes mightalso have a higher angiotensin converting enzyme-2 (ACE2) expression, thereby facilitating viral uptake and increasing the risk of severe infection [6,7]. However, further research is required to better understand the link between diabetes and the viral disease process.

Table 1
Main clinical and biochemical characteristics of middle-aged patients with laboratory-confirmed COVID-19, stratified by diabetes status at hospital admission.

	Without diabetes	With diabetes	*P* value
n	280	59	
Age (years)	46.5 ± 15.7	57.0 ± 11.7	< 0.0001
Male sex (%)	46.1	52.5	0.392
BMI (kg/m^2)	23.8 ± 3.6	25.0 ± 4.3	0.034
BMI ≥ 25 kg/m^2 (%)	35.0	54.2	0.008
Current smokers (%)	8.9	5.1	0.440
Systolic blood pressure (mmHg)	131 ± 16	135 ± 18	0.098
Diastolic blood pressure (mmHg)	81 ± 11	80 ± 10	0.640
Hypertension (%)	16.8	54.2	< 0.0001
White blood count (× 10^9/L)	4.78 (3.8–6.2)	5.31 (4.3–7.1)	0.028
Neutrophil count (× 10^9/L)	3.02 (2.2–4.1)	3.60 (2.8–5.1)	< 0.005
Lymphocyte count (× 10^9/L)	1.20 (0.9–1.6)	1.01 (0.6–1.3)	< 0.005
Haemoglobin (g/L)	133.1 ± 15	131.8 ± 18	0.559
Platelet count (× 100,000/mm^3)	200 ± 71	216 ± 89	0.148
Prothrombin time (sec)	12.0 ± 1.5	12.5 ± 1.2	0.062
Activated partial thromboplastin time (sec)	32.1 ± 4.3	33.1 ± 4.9	0.172
D-dimer (mg/L), *n* = 200	0.18 (0.11–0.30)	0.51 (0.2–0.8)	< 0.001
C-reactive protein (mg/L)	11.2 (2.5–31)	14.1 (5–45)	0.078
Procalcitonin (ng/mL), *n* = 190	0.06 (0.03–0.25)	0.05 (0.04–0.11)	0.819
Albumin (g/L), *n* = 231	41.5 (38.3–43.9)	36.7 (31.6–42.1)	< 0.001
Total bilirubin (μmol/L)	10.8 (7.3–15.6)	12.4 (9.0–16.7)	0.162
AST (IU/L)	23 (19–32)	29 (21–39)	0.015
ALT (IU/L)	21 (14–31)	24 (20–42)	< 0.005
ALP (IU/L)	57 (48–73)	62 (50–82)	0.205
GGT (IU/L)	23 (15–43)	33 (24–51)	< 0.005
Creatinine (μmol/L)	65.2 ± 16.9	65.6 ± 17.2	0.897
Random plasma glucose (mmol/L)	6.11 ± 1.5	10.2 ± 4.8	< 0.0001
Haemoglobin A1c (mmol/mol), *n* = 57	39.9 ± 2.3	60.1 ± 5.0	< 0.0001
Total cholesterol (mmol/L)	3.98 ± 0.9	3.84 ± 0.8	0.261
Triglycerides (mmol/L)	1.22 (0.9–1.7)	1.28 (1.1–1.9)	0.106
HDL-cholesterol (mmol/L)	1.15 ± 0.3	1.01 ± 0.3	< 0.005
LDL-cholesterol (mmol/L)	2.27 ± 0.8	2.11 ± 0.7	0.156
Hospital stay (days)	18 (13–24)	19 (13–25)	0.514
Severity of COVID-19 illness			< 0.0001
Mild (%)	5.0	3.4	
Moderate (%)	80.7	57.6	
Severe (%)	11.4	28.8	
Critical (%)	2.9	10.2	

Cohort size, *n* = 339, except where indicated. Presence of diabetes was defined as prior history of diabetes (including current use of any glucose-lowering medication), a "random" plasma glucose level ≥ 11.1 mmol/L (≥ 200 mg/dL), and/or a haemoglobin A1c level ≥ 6.5% (≥ 48 mmol/mol). Data are expressed as means ± SD, medians and IQRs (in parenthesis) or percentages. Differences between the two groups were tested by the chi-squared test or the Fisher's exact test for categorical variables (as appropriate), the unpaired Student's *t* test for normally distributed continuous variables, or the Mann–Whitney U test for non-normally distributed continuous variables, respectively. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; GGT: gamma-glutamyltransferase; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

Our study has some limitations that should be mentioned, including the relatively modest sample size, the Asian ancestry of the patient cohort, and the lack of any detailed information on glucose-lowering medications, and type of diabetes (though it is reasonable that the vast majority of our diabetic cases were likely to be type 2). Thus, our results need to be further replicated in other Asian and non-Asian cohorts of COVID-19 patients.

In conclusion, we found that in hospitalised middle-aged Chinese patients with laboratory-confirmed COVID-19, the presence of diabetes at hospital admission was strongly associated with an increased likelihood of having severe COVID-19 illness. We also observed a graded, positive relationship between random blood glucose levels at admission and severity of COVID-19 illness. Notably, the significant association between diabetes and risk of greater COVID-19 severity persisted even after adjustment for age, sex, smoking history and metabolic comorbidities. Our findings highlight the urgent need of a multidisciplinary team-based approach to the management of these patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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Metformin misuse in chronic kidney disease

Diabetes affects 450 million people around the world and is expected to reach 693 million people by 2045 [1]. One of every three patients with diabetes also presents with chronic kidney disease (CKD) [2]. Metformin is the first-line therapy for patients with type 2 diabetes mellitus (T2DM) and reduces the risk of cardiovascular events and death [3], including CKD patients [4]. However, metformin has side-effects, mainly lactic acidosis in CKD, and this may represent a limitation to its prescription. However, several national and international organizations have recently modified metformin contraindications, expanding its use in CKD down to those with an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2, as published in 2016 by the Kidney Disease: Improving Global Outcomes (KDIGO) organization [5] and US Food and Drug Administration (FDA) [6]. This means that metformin can now be prescribed in CKD down to the 3B stage, a stage in which metformin has been shown to be associated with a reduction in mortality. Yet, metformin prescriptions for CKD have never been precisely described for everyday clinical practice since the recent development of these recommendations and, in particular, not for the non-contraindicated CKD stages for which metformin use was banned by physicians because of the widely delivered warning about lactic acidosis. Thus, the aim of the present study was to describe the use of metformin in CKD patients in everyday clinical practice.

Our retrospective cohort study used data from nephrology consultations that took place between March 2014 and March 2016 at the University Hospital Centre Hospitalier Lyon Sud in Lyon, France. Exclusion criteria were: non-T2DM patients ($n = 49$); patients undergoing maintenance dialysis; kidney transplant patients ($n = 12$); and patients aged < 18 years. Of the initial 911 diabetes patients, 61 fulfilled the exclusion criteria and 269 were missing data, thus leaving 581 patients for inclusion, for whom HbA_{1c} was recorded in 376 of them. Clinical and biological data were also recorded.

Metformin prescriptions were analyzed to calculate the proportion of patients treated with metformin at each CKD stage, with descriptions of their daily doses. Their antidiabetic treatments were described according to three categories: patients treated with metformin; patients treated with insulin; and patients treated with other antidiabetic treatments, including sulphonylureas, glinides, alpha-glucosidase inhibitors, glucagon-like peptide (GLP)-1 analogues and dipeptidyl peptidase (DPP)-4 inhibitors. Basic statistics pertaining to the study population are presented as % (n) and means ± standard deviation (SD). Comparisons were performed by Student's t test using Excel (2016 version) software (Microsoft Corporation, Redmond, WA, USA).

Baseline characteristics revealed that metformin users were significantly younger than non-metformin users (64.6 years vs 72.3 years, respectively; $P < 0.001$), whereas body mass index (BMI) scores were similar in both groups (32.0 kg/m^2 vs 31.2 kg/m^2; $P = 0.31$). Metformin prescription was more frequent for men than for women (37% vs 26%, respectively; $P = 0.004$), although mean daily doses were similar in both genders (1643 mg/day vs 1680 mg/day, respectively; $P = 0.72$). Women had lower mean

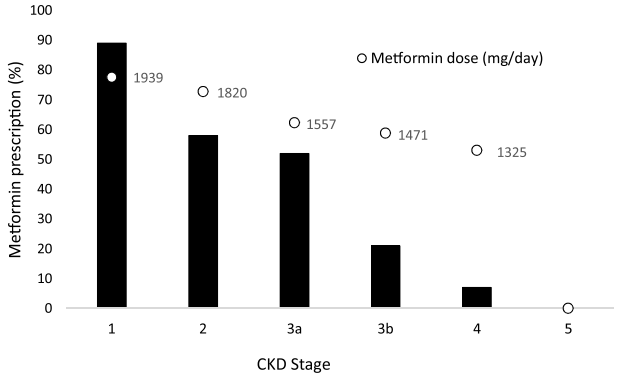

Fig. 1. Proportions of metformin prescriptions at every stage of chronic kidney disease (CKD).

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