Dear Editor,

Since the first discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and description of the coronavirus disease 2019 (COVID-19), a pandemic has evolved. Due to winter tourism, Tyrol, a federal province of Austria with 750,000 inhabitants, has emerged as an epicenter in Austria being faced with a surge of critically ill COVID-19 patients reaching its peak on April 8, 2020.

We retrospectively analyzed the incidence of diabetes in all critically ill patients admitted to the four dedicated COVID-19 intensive care units (ICU) at the University Hospital in Innsbruck, Tyrol, Austria, which covers 180,000 inhabitants as primary hospital and also functions as a tertiary referral center for the whole region of Tyrol. Patients were included in the analysis if they were 18 years of age or older, had confirmed COVID-19, and were admitted to an intensive care unit from March 11 to April 29, 2020. COVID-19 was confirmed by reverse-transcriptase-polymerase-chain-reaction assays of nasopharyngeal swab specimens. Data were abstracted manually from electronic and paper-based health records. Glycated hemoglobin (HbA1c) was measured on admission by high-performance liquid chromatography (HPLC-UV/VIS).

Of 47 COVID-19 patients admitted to our ICUs, HbA1c was measured in 44, which were included in the analysis (Table 1). The median age of patients was 61.5 (IQR 53.0–68.0). Thirty-five (80%) patients required invasive mechanical ventilation (IMV). Additionally, 4 patients (9%) required veno-venous extracorporeal membrane oxygenation (vvECMO). At the time of writing this article, 11 patients (25%) have died in the hospital, 25 (56.8%) have been discharged alive from the ICU, 20 patients (45.5%) were discharged alive from the hospital, and 13 patients (29.5%) are still hospitalized.

Median HbA1c was 6.5% (IQR 6.1–6.7%). When categorizing patients according to HbA1c [<1], 24 (54.5%) were considered to have diabetes mellitus (HbA1c ≥ 6.5%), 16 (36.3%) were considered to have prediabetes (HbA1c ≥ 5.7% < 6.5%), and only 4 (9%) had no diabetes (HbA1c < 5.7%). Interestingly, only 7 (15.9%) patients showed a medical history of diabetes mellitus. Five (11.4%) patients had previously been treated with antidiabetic medication, and no patient had required insulin prior to hospitalization. Patients with increased HbA1c levels developed higher maximum CRP and IL-6 levels during their ICU stay. There was a trend to higher in-hospital mortality with increasing HbA1c.

The median body mass index (BMI) was 29.4 kg/m² (IQR 26.2–32.7), which is slightly higher than a previously studied sample of critically ill patients in Austria [2], with a median BMI of 26 kg/m². BMI did not differ significantly between diabetic and non-diabetic patients (Fig. 1).

In conclusion, 85% of COVID-19 treated in our intensive care units had prediabetes and diabetes which appear to be predisposing factors for severe manifestations of COVID-19, potentially impairing outcome. This is in line with previous observations from the first SARS-CoV epidemic [3].

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Hyperglycemia may alter the response of the innate immune system through several mechanisms. It may induce Toll-like receptor expression and inhibit neutrophil function, decrease vascular dilation, and increase permeability [4]. Furthermore, it can cause direct glycosylation of proteins, thereby altering the structure of complement, and may cause a cytokine storm [4, 5]. Recent data demonstrating viral particles in endothelial cells of several organs suggest "endotheliitis" as a possible mechanism of organ dysfunction leading to critical illness in COVID-19 patients which may be aggravated by endothelial

| Characteristic | Total (N = 44) | HbA1c < 5.7% (N = 4) | HbA1c ≥ 5.7 < 6.5% (N = 16) | HbA1c ≥ 6.5% (N = 24) |
|---------------|---------------|-----------------------|-----------------------------|------------------------|
| Age—median (IQR) [years] | 61.5 (53.0–68.0) | 53.5 (43.8–64.0) | 64 (53.8–68.0) | 59 (53.8–69.8) |
| Male sex—no. (%) | 32 (72) | 3 (75) | 13 (81) | 16 (66) |
| Caucasian race—no. (%) | 32 (72) | 3 (75) | 13 (81) | 16 (66) |
| BMI—median (IQR) [kg/m²] | 29.4 (26.2–32.7) | 27.8 (24.9–30.6) | 27.7 (25.5–34.8) | 29.5 (26.9–32.6) |
| HbA1c—median (IQR) [%] | 6.5 (6.1–6.7) | 5.6 (5.5–5.6) | 6.2 (5.9–6.3) | 6.7 (6.6–7.1) |
| Maximum CRP—median (IQR) [mg/dl] | 31.5 [20.5–35.5] | 18.3 [16.9–20.9] | 29.8 [19.7–35.9] | 33.0 [22.4–35.8] |
| Maximum IL-6—median (IQR) [ng/l] | 797.9 [381.7–1886.3] | 284.9 [212.2–383.2] | 1097.4 [403.8–2200.3] | 851.9 [419.3–2156.3] |

Known comorbidity*—no. (%)

- Metabolic syndrome 8 (18) 0 (0.0) 4 (25) 4 (17)
- Prediabetes 0 (0) 0 (0) 0 (0) 0 (0)
- Diabetes mellitus type I 0 (0) 0 (0) 0 (0) 0 (0)
- Diabetes mellitus type II 7 (15) 1 (25) 0 (0) 6 (25)
- Cardiovascular 11 (25) 2 (50) 2 (13) 7 (29)
- Hypertension 19 (43) 2 (50) 7 (44) 10 (42)
- Renal 6 (13) 0 (0) 3 (19) 3 (13)
- Liver 4 (9) 0 (0) 2 (13) 2 (8)
- Metastatic disease 0 (0) 0 (0) 0 (0) 0 (0)
- Hematological malignancy 2 (4) 0 (0) 2 (13) 0 (0)
- Non-hematological malignancy 3 (7) 1 (25) 2 (13) 0 (0)
- Immunosuppression 5 (11) 0 (0) 3 (19) 2 (8)
- COPD 6 (13) 0 (0) 2 (13) 4 (17)
- Asthma 4 (9) 1 (25) 2 (13) 1 (4)
- Respiratory disease—others 4 (9) 1 (25) 3 (19) 0 (0)
- Neurologic comorbidity 3 (7) 1 (25) 2 (13) 0 (0)
- Chest radiographic findings consistent with viral pneumonia—no. (%) 43 (98) 4 (100) 16 (100) 23 (96)
- SARS-CoV-2-PCR positive—no. (%) 44 (100) 4 (100) 16 (100) 24 (100)
- Invasive mechanical ventilation—no. (%) 35 (80) 2 (50) 13 (81) 20 (84)
- Veno-venous extracorporeal membrane oxygenation—no. (%) 4 (9) 1 (25) 1 (6) 3 (13)
- Death in hospital—no. (%) 11 (25) 0 (0) 4 (25) 7 (29)

Abbreviations: IQR interquartile range, BMI body mass index, HbA1c glycated hemoglobin, CRP C-reactive protein, IL-6 interleukin-6, COPD chronic obstructive pulmonary disease, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

*If specified in the patients’ health records
dysfunction associated with prediabetes and diabetes [6]. More pronounced peak levels of inflammation observed in our patients with abnormal HbA1c may support such an assumption. In conclusion, we recommend routine measurement of HbA1c in hospitalized COVID-19 patients for additional risk stratification, because most patients of our cohort were previously not diagnosed with having impaired glucose tolerance.

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SJK, SK, and MJ collected data and wrote the manuscript. DF, SM, and CT collected data for this study. The author(s) read and approved the final manuscript.

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Availability of data and materials
No data is publicly available at this time.

Ethics approval and consent to participate
This study was approved by the ethics committee of the Medical University Innsbruck (# 1099/2020).

Consent for publication
Not applicable—the manuscript contains no individual patient data.

Competing interests
None of the authors have any conflicts of interest to declare.

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