Case-control Investigation of Previously Undiagnosed Diabetes in the Critically Ill

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Abstract

Context: The outcome of patients requiring intensive care can be influenced by the presence of previously undiagnosed diabetes (undiagDM).

Objective: This work aimed to define the clinical characteristics, glucose control metrics, and outcomes of patients admitted to the intensive care unit (ICU) with undiagDM, and compare these to patients with known DM (DM).

Methods: This case-control investigation compared undiagDM (glycated hemoglobin A1c [HbA1c] ≥ 6.5%, no history of diabetes) to patients with DM. Glycemic ratio (GR) was calculated as the quotient of mean ICU blood glucose (BG) and estimated preadmission glycemia, based on HbA1c ($$[28.7 \times HbA1c] + 48.7 \text{ mg/dL}$$). GR was analyzed by bands: less than 0.7, 0.7 to less than or equal to 0.9, 0.9 to less than 1.1, and greater than or equal to 1.1. Risk-adjusted mortality was represented by the Observed-Expected mortality ratio (OEMR), calculated as the quotient of observed mortality and mortality predicted by the severity of illness (APACHE IV prediction of mortality).

Results: Of 5567 patients 294 (5.3%) were undiagDM. UndiagDM had lower ICU mean BG ($$P < .0001$$) and coefficient of variation ($$P < .0001$$) but similar rates of hypoglycemia ($$P = .08$$). Mortality and risk-adjusted mortality were similar in patients with GR less than 1.1 comparing undiagDM and DM. However, for patients with GR greater than or equal to 1.1, mortality (38.5% vs 10.3% $$P = .0072$$) and risk-adjusted mortality (OEMR 1.18 vs 0.52 $$P < .0001$$) were higher in undiagDM than in DM.

Conclusion: These data suggest that DM patients may develop tolerance to hyperglycemia that occurs during critical illness, a protective mechanism not observed in undiagDM, for whom hyperglycemia remains strongly associated with higher risk of mortality. These results may shed light on the natural history of diabetes.

Key Words: diabetes, hyperglycemia, hypoglycemia, mortality, critically ill, glycemic ratio

Abbreviations: APIV PM, Acute Physiology and Chronic Health Evaluation IV predicted mortality; BG, blood glucose; CON, conventional insulin therapy; CV, coefficient of variation; DCCT, Diabetes Control and Complications Trial; DM, diabetes mellitus; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA1c, glycated hemoglobin A1c; GR, glycemic ratio; ICU, intensive care unit; INS, insulin; INT, intensive insulin therapy; IQR, interquartile range; IV, intravenous; OEMR, observed:expected mortality ratio; undiagDM, previously undiagnosed diabetes mellitus.

The prevalence of diabetes (DM) is increasing worldwide. Recent data suggest that the age-standardized prevalence has increased in the United States from 9.8% of the population in 1999 to 2000 to 14.3% in 2017 to 2018 [1]. The percentage of hospitalized patients with DM is considerably higher, owing to the high burden of comorbidities associated with this disease [2]. Hyperglycemia can also occur in hospitalized patients not previously diagnosed with DM, especially among those admitted with critical illness. For these patients, the association between hyperglycemia and hospital outcome is different from that for patients previously known to have DM [3–8]. Among patients without DM, higher mean blood glucose (BG) during intensive care unit (ICU) admission has been consistently demonstrated to be associated with higher mortality [3–8]. In contrast, the relationship between mean ICU BG and mortality for DM patients is not consistent [3–8]. Recent literature has demonstrated the importance of preadmission glycemia, reflected by glycated hemoglobin A1c (HbA1c) levels. For patients with low HbA1c, high mean ICU BG is strongly associated with high mortality, but the opposite is seen for patients with high HbA1c at admission, for whom high mean ICU BG is associated with lower mortality [9–18].

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Many patients admitted to the ICU without a previous diagnosis of DM who, based on measurement of HbA1c at the time of ICU admission, are diagnosed as having DM after hospital admission, referred to herein as previously undiagnosed DM (undiagDM) [19–24]. Previous studies have not provided detailed information about comorbidities, or glucose metrics and their relationships to outcome for this subset.

The purpose of this investigation is to delineate clinical characteristics, glucose metrics, and mortality of patients admitted to a mixed medical-surgical ICU with undiagDM, based on HbA1c greater than or equal to 6.5% obtained at or near ICU admission. We used case-control methodology to compare this group of patients to those with previously diagnosed DM. We hypothesized that (1) glucose metrics during ICU admission would differ between the 2 groups and (2) that the relationship of ICU glucose metrics to risk-adjusted mortality would be different for undiagDM and patients with known DM.

Materials and Methods

Patients and Study Center

This investigation includes adult patients admitted consecutively to the 20-bed Stamford Hospital ICU with at least 4 BG levels obtained during ICU admission and HbA1c level obtained at admission, or within 3 months of admission. The study excludes patients younger than 18 years, patients admitted with diabetic ketoacidosis or hyperglycemic hyperosmolar state, and patients admitted following cardiovascular surgery (because of their very low mortality). Fig. 1 details the flow of included and excluded patients.

The center is a teaching hospital associated with Columbia University College of Physicians and Surgeons. The ICU cares for a broad array of medical and surgery patients; organ transplantation is not performed. Care is delivered by multidisciplinary teams led by medical and surgical intensivists; nursing-to-patient ratio is 1:2 or 1:1, based on acuity and severity of illness.

Case-Control Methodology

Patients with a history of diabetes were prospectively identified at the time of ICU admission (DM). Those with newly diagnosed diabetes (undiagDM) were defined as having an HbA1c greater than or equal to 6.5% but no prior history of diabetes.

A total of 294 patients were identified as undiagDM. Two investigators (Y.W. and J.B.), unaware of other patient comorbidities, glucose control metrics, or clinical outcomes, performed 1:1 matches of undiagDM with appropriate DM matches using 3 criteria:

- HbA1c 6.5% to 7.9% or HbA1c greater than or equal to 8.0%;
- admission to the ICU with a medical or surgical diagnosis; or
- admission to the ICU before or after the change in BG treatment protocols.

Glucose Control Strategy

Details of the ICU’s glucose control protocol have been published previously [25]. In brief, before October 14, 2014, all patients had a BG target range of 90 to 125 mg/dL. After this date “tight” (80-140 mg/dL) or “loose” (110-160 mg/dL) BG target ranges were chosen based on HbA1c less than 7.0% or greater than or equal to 7.0%, respectively. Continuous intravenous (IV) regular insulin infusion was initiated when BG exceeded 180 mg/dL on 2 successive readings. Mild hyperglycemia in the 140 to 180 mg/dL range was treated with short-acting subcutaneous analogue insulin injections. The protocol mandated monitoring frequency as every 3 hours for all patients and every hour if the patient was treated with IV insulin. While arterial or venous blood was used preferentially, capillary blood was also tested. Measurement technology included the GEM 4000 arterial blood gas analyzer (Instrument Laboratories) or Accu-Chek Inform II glucometer (Roche Diagnostics).

### Figure 1

Derivation of the patient cohorts, including dates of admission, inclusions, and exclusions.
The ICU's comprehensive database including demographics, admitting diagnoses, severity of illness scores and clinical outcomes, was maintained manually by one of the authors (J.K.) through December 31, 2018. After this date these data were abstracted automatically by the Phoenix data management system (Medical Decisions Network). BG values, including all point-of-care data, were abstracted from the hospital’s

### Table 1. Clinical characteristics and outcomes of known diabetes mellitus patients and previously undiagnosed diabetes mellitus patients

|                      | DM     | undiagDM | P       |
|----------------------|--------|----------|---------|
| No.                  | 294    | 294      |         |
| Age, y               | 72 (60-82) | 68 (59-79) | .0117   |
| Male, %              | 53.7   | 62.9     | .0238   |
| BMI                  | 28.9 (25.0-34.1) | 28.1 (24.5-34.0) | .23 |
| eGFR, % of patients, mL/min/1.73 m² |         |         |         |
| > 60                 | 46.6   | 60.2     | .0010   |
| 40-59                | 21.1   | 19.0     | .53     |
| 20-39                | 16.3   | 13.6     | .36     |
| < 20                 | 16.0   | 7.1      | .0007   |
| Comorbidities, %     |        |          |         |
| Current smoker       | 8.2    | 11.2     | .22     |
| Past smoker          | 39.8   | 34.0     | .15     |
| Hypertension         | 83.3   | 68.0     | <.0001  |
| Hyperlipidemia       | 78.2   | 60.5     | <.0001  |
| Coronary artery disease | 54.1  | 33.0     | <.0001  |
| Cerebrovascular disease | 25.2  | 24.8     | .91     |
| Peripheral vascular disease | 29.3 | 12.6     | <.0001  |
| Preadmission meds, % |        |          |         |
| Statins              | 68.4   | 52.0     | <.0001  |
| ARB/ARB              | 50.7   | 29.9     | <.0001  |
| Insulin              | 48.3   | N/A      |         |
| Metformin            | 32.7   | N/A      |         |
| Sulfonylureas        | 21.5   | N/A      |         |
| SGLT2                | 1.7    | N/A      |         |
| GLP1                 | 1.4    | N/A      |         |
| DPP-4                | 17.0   | N/A      |         |
| Diagnostic categories|        |          |         |
| Medical              | 77.9   | 77.9     | .13     |
| Cardiac              | 28.2   | 22.8     |         |
| Respiratory          | 20.7   | 19.0     | .61     |
| Neurologic           | 10.6   | 10.2     | .87     |
| Septic shock         | 9.9    | 10.9     | .69     |
| Gastrointestinal     | 4.1    | 7.5      | .0781   |
| Other                | 4.4    | 7.5      | .11     |
| Surgical/trauma, %   | 22.1   | 22.1     |         |
| Vascular             | 6.5    | 5.1      | 0.47    |
| Gastrointestinal     | 6.1    | 4.8      | .49     |
| Neurologic           | 2.4    | 3.4      | .47     |
| Respiratory          | 1.0    | 2.7      | .13     |
| Other                | 2.7    | 1.7      | .41     |
| Trauma               | 3.4    | 4.4      | .53     |
| ICU LOS, d           | 1.9 (1.1-3.9) | 2.0 (1.0-4.2) | .91 |
| APACHE IV predicted mortality, % | 22.5 (1.4) | 23.2 (1.5) | .75 |
| Mortality, %         | 13.6   | 16.7     | .29     |
| Observed:expected mortality ratio | 0.60 | 0.72 | .0021 |

Abbreviations: ARB/ARB, angiotensin-converting enzyme/angiotensin receptor blockade; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; DM, known diabetes patients; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; LOS, length of stay; GLP-1, glucagon-like peptide 1; ICU, intensive care unit; SGLT2, sodium-glucose cotransporter 2; undiagDM, previously undiagnosed diabetes patients.
Risk-adjusted mortality was represented by the observed: expected mortality ratio (OEMR), calculated using the Acute Physiology and Chronic Health Evaluation IV predictions of mortality (APIV PM) [26]; OEMR equals the quotient of observed mortality percentage and the mean APIV PM, with ratios less than 1 indicating that the patient cohort had a lower mortality rate than the model predicted and ratios greater than 1 indicating that the patient cohort had a higher mortality rate than the model predicted. We compared these ratios using the Z test for independent proportions for between-group comparisons [27].

The APACHE IV model calculates an individual patient’s prediction of mortality before hospital discharge based on a large number of different parameters: age; 15 vital sign and laboratory values derived from the first 24 hours of ICU admission; the Glasgow Coma Scale, for assessment of neurologic status; a discrete group of comorbidities (AIDS, cirrhosis, hepatic failure, immunosuppression, lymphoma, leukemia or myeloma, metastatic tumor); ICU admission diagnosis (n = 116); ICU admission source (general ward, emergency room, operating/recovery room, stepdown unit, direct admission, other ICU, other hospital); the length of stay in the hospital before ICU admission; and mechanical ventilation. The model does not include diabetes among the comorbidities as it did not contribute to the model’s precision; maximum BG greater than or equal to 300 during the first 24 hours contributes a very small amount to the score.

We calculated glycemic ratio (GR) [18], a metric that describes the extent of divergence of acute glycemia from preadmission glycemia, as the quotient of mean ICU BG and estimated preadmission BG, using the Nathan formula based on HbA1c ([28.7 × HbA1c] – 46.7 mg/d) [28]. We stratified the relationship between GR and mortality as well as GR and risk-adjusted mortality, represented by OEMR, by the bands of GR less than 0.7, 0.7 to 0.9, 0.9 to 1.1 and 1.1 or greater. A P value of less than .05 was considered statistically significant.

We used MedCalc Statistical Software (version 18.11.6) for statistical analysis (MedCalc Software bvba; https://www.medcalc.org; 2019).

Results

Of 5567 patients who met inclusion criteria during the period of the investigation, 3721 (66.8%) had no prior history of diabetes and an HbA1c less than 6.5%, 1552 (27.9%) had a history of diabetes (DM), and 294 (5.3%) were undiagDM (see Fig. 1). Table 1 displays clinical characteristics of undiagDM and their DM matches. Patients with DM were older and less likely to be male than were undiagDM. They were more likely to have hypertension, hyperlipidemia, coronary artery disease, and peripheral vascular disease and their renal function was worse than were undiagDM.

Although hospital mortality was statistically similar between the 2 groups, undiagDM had higher risk-adjusted mortality (represented by OEMR) than did DM.

Table 2 details glucose metrics for the 2 groups. Patients with DM had higher mean BG and higher coefficient of variation (CV) than did undiagDM and a higher percentage received insulin in the ICU.

Table 3 compares the 227 undiagDM with HbA1c 6.5% to 7.9% to the 67 undiagDM with an HbA1c greater than or

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**Table 2. Glucose metrics of known diabetes patients and previously undiagnosed diabetes mellitus patients**

| Metric                                      | DM                        | undiagDM                  | P      |
|---------------------------------------------|----------------------------|----------------------------|--------|
| Mean blood glucose, mg/dL                   | 151 (136-171)             | 138 (123-158)             | <.0001 |
| Coefficient of variation, %                 | 27.4 (20.7-34.8)          | 21.7 (16.3-29.5)          | <.0001 |
| Hypoglycemia < 70 mg/dL                     | 23.8                      | 18.0                      | .0840  |
| IV insulin received in ICU<sup>a</sup>      | 52.0                      | 28.6                      | <.0001 |
| SC insulin received in ICU<sup>a</sup>      | 89.5                      | 81.6                      | .0065  |
| No. of blood glucose tests in ICU           | 22 (11-57)                | 16 (8-48)                 | .0045  |
| HbA1c, %                                    | 7.2 (6.7-7.9)             | 6.9 (6.6-7.8)             | .0007  |
| Glycemic ratio                              | 0.91 (0.79-1.01)          | 0.86 (0.76-0.97)          | .0081  |

**Abbreviations:** DM, known diabetes patients; HbA1c, glycated hemoglobin; CV, coefficient of variation; ICU, intensive care unit; SC, subcutaneous; undiagDM, previously undiagnosed diabetes patients.

<sup>a</sup>Percentage of patients.

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**Table 3. Comparison of previously undiagnosed diabetes patients with glycated hemoglobin A<sub>1c</sub> 6.5% to 7.9% and 8.0% or greater**

| Metric                                      | HbA1c 6.5%-7.9% | HbA1c ≥ 8.0% | P      |
|---------------------------------------------|-----------------|--------------|--------|
| No.                                          | 227             | 67           |        |
| Mean blood glucose, mg/dL                   | 134 (121-153)   | 153 (137-181)| <.0001 |
| Coefficient of variation, %                 | 20.3 (15.4-26.2)| 29.5 (22.0-36.9)| <.0001 |
| Hypoglycemia < 70 mg/dL                     | 17.2            | 20.9         | .49    |
| IV insulin received in ICU<sup>a</sup>      | 21.1            | 53.7         | <.0001 |
| SC insulin received in ICU<sup>a</sup>      | 79.3            | 89.6         | .0561  |
| No. of blood glucose tests in ICU           | 15 (7-46)       | 20 (9-54)    | .24    |
| HbA1c, %                                    | 6.7 (6.6-7.1)   | 9.1 (8.3-10.5)| <.0001 |
| Glycemic ratio                              | 0.90 (0.81-0.99)| 0.72 (0.60-0.79)| <.0001 |
| Male, %                                     | 61.7            | 67.1         | .42    |
| APACHE IV predicted mortality, %            | 29.5 (7.6)      | 18.0 (22.4)  | <.0001 |
| ICU LOS, d                                  | 1.9 (1.0-5.1)   | 2.0 (1.0-3.9)| .77    |
| Mechanical ventilation, %                   | 44.9            | 32.8         | .0785  |
| Mortality                                   | 18.1            | 11.9         | .23    |
| Observed:Expected mortality ratio           | 0.61            | 0.66         | .46    |

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; DM, diabetes patients; HbA1c, glycated hemoglobin A<sub>1c</sub>; IV, intravenous; ICU, intensive care unit; SC, subcutaneous; undiagDM, previously undiagnosed diabetes patients.

<sup>a</sup>Percentage of patients.
equal to 8.0%. The latter group had higher mean ICU BG and CV and a higher percentage received insulin in the ICU.

Table 4 describes the relationship of hypoglycemia to mortality for undiagDM and DM. Mortality was significantly higher among patients with hypoglycemia in both cohorts. Risk-adjusted mortality was higher in both cohorts with hypoglycemia less than 55 mg/dL than with hypoglycemia 55 to 69 mg/dL.

Finally, Figs. 2A and 2B illustrate the association of GR, the quotient of mean ICU BG and estimated preadmission BG, with mortality, and the risk-adjusted mortality (represented by OEMR). Absolute as well as risk-adjusted mortality were similar for the 2 groups in the broad range of GR 0.7 to less than or equal to 1.1. However, for patients with GR greater than or equal to 1.1, mortality (38.5% vs 10.3% [P = .0072]) and risk-adjusted mortality (OEMR 1.18 vs 0.52 [P < .0001]) were considerably higher in undiagDM than in DM, though there were no statistically significant differences in mean BG, CV, or hypoglycemia between the 2 groups (Table 5).

Discussion
To our knowledge, this is the first investigation that explores glucose metrics and their relationship to mortality among a cohort of critically ill patients with previously undiagnosed DM (undiagDM). The salient findings of this case-control study include the following:

- Risk-adjusted mortality was higher in undiagDM than in DM, attributable to a markedly higher mortality among patients with GR (the quotient of mean ICU BG and estimated preadmission BG, using the Nathan formula [28]) greater than or equal to 1.1 in this group.
- UndiagDM had a significantly lower burden of comorbidities, including hypertension, hyperlipidemia, coronary artery disease, peripheral vascular disease, and renal insufficiency, at the time of admission than did DM.
- UndiagDM had lower mean BG, lower CV, and a trend toward lower percentage of patients with hypoglycemia less than 70 mg/dL than did DM.
- Hypoglycemia less than 70 mg/dL was associated with higher risk-adjusted mortality in undiagDM but not in DM. Hypoglycemia less than 55 mg/dL was associated with higher risk-adjusted mortality in undiagDM but not in DM. Hypoglycemia less than 55 mg/dL was associated with higher risk-adjusted mortality in both cohorts.

Relationship to Prior Literature
Prevalence of previously undiagnosed diabetes
Several prior studies have identified undiagDM in hospitalized patients using HbA1c obtained at admission, or follow-up glucose tolerance tests [19–24], with percentages ranging from 9.3% [20] to 24% [21]. In contrast, the present investigation identified 5.3% with undiag DM. It is possible that the lower prevalence of undiag DM in our cohort is due to a high intensity of outpatient care in the community.

Glucose metrics and mortality of previously undiagnosed diabetes
In a single-center cohort of 1886 non-ICU patients, Umpierrez and colleagues [29] identified 26% with known DM and 12% with no prior diagnosis of DM but with a fasting BG greater than 126 mg/dL.

Table 4. Mortality and severity-associated mortality stratified by severity of hypoglycemia

|            | No. | Mortality % | APACHE IV predicted mortality, % | Observed: Expected mortality ratio | P Mortality | P Observed: Expected mortality ratio |
|------------|-----|-------------|----------------------------------|------------------------------------|-------------|-------------------------------------|
| DM         |     |             |                                  |                                    |             |                                     |
| No hypoglycemia | 224 | 10.7        | 18.9                             | 0.57                               |             |                                     |
| Hypoglycemia: Minimum BG, mg/dL | | | | | | |
| < 70       | 70  | 22.9        | 34.1                             | 0.67                               | .0080       | .14                                 |
| 55-69      | 48  | 22.9        | 37.4                             | 0.61                               | .0222       | .61                                 |
| < 55       | 22  | 22.7        | 27.0                             | 0.84                               | .0963       | .0139                               |
| 40-54      | 19  | 21.1        | 27.2                             | 0.78                               |             |                                     |
| < 40       | 3   | 33.3        | 25.5                             | 1.31                               |             |                                     |
| undiagDM   |     |             |                                  |                                    |             |                                     |
| No hypoglycemia | 241 | 12.4        | 19.5                             | 0.64                               |             |                                     |
| Hypoglycemia: Minimum BG, mg/dL | | | | | | |
| < 70       | 53  | 35.9        | 40.2                             | 0.89                               | <.0001      | .0004                               |
| 55-69      | 33  | 21.2        | 33.2                             | 0.64                               | .17         | ≥.999                               |
| < 55       | 20  | 60.0        | 51.8                             | 1.16                               | <.0001      | <.0001                              |
| 40-54      | 15  | 60.0        | 45.8                             | 1.31                               |             |                                     |
| < 40       | 5   | 60.0        | 70.0                             | 0.86                               |             |                                     |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BG, blood glucose; DM, diabetes patients; undiagDM, previously undiagnosed diabetes patients.

a Hypoglycemia vs no hypoglycemia.
than 126 mg/dL or 2 random values greater than 200 mg/dL; this group of patients sustained markedly higher mortality (16.0%) than did the groups with no diabetes (1.7%). A multicenter ICU study found that undiagDM had higher mean ICU BG, CV, hypoglycemia, and mortality than did patients without DM [21]. In addition, this study stratified the known DM cohort based on HbA₁c less than or greater than or equal to 6.5%. The undiagDM cohort had values of mean ICU BG, CV, and hypoglycemia intermediate between DM patients with HbA₁c less than 6.5% and those with HbA₁c greater than or equal to 6.5% in this study.

**Biologic Plausibility**

In this case-control study, higher mean ICU BG in the undiagDM cohort was associated with higher mortality,
Table 5. Comparison of known diabetes patients and previously undiagnosed diabetes patients stratified by bands of glycemic ratio

| GR | GR<0.7 | undiagDM | P  |
|----|--------|-----------|----|
| No. | 33     | 44        | .67|
| Age, y | 62 (54-78) | 64 (55-74) | .79|
| Male, % | 60.6 | 63.6 | .84|
| BMI | 28.4 (23.7-33.5) | 27.6 (23.7-34.4) | .84|
| eGFR, % of patients | | | |
| > 60 | 48.5 | 61.4 | .26|
| 40-59 | 9.1 | 20.5 | .18|
| 20-39 | 21.2 | 13.6 | .38|
| < 20 | 21.2 | 4.5 | .0248|
| Comorbidities, % of patients | | | |
| Current smoker | 3.0 | 18.2 | .0412|
| Past smoker | 42.2 | 25.0 | .11|
| Hypertension | 84.8 | 61.4 | .0254|
| Hyperlipidemia | 81.8 | 45.5 | .0013|
| CAD | 39.4 | 31.8 | .49|
| Cerebrovascular disease | 33.3 | 20.5 | .21|
| Peripheral vascular disease | 24.2 | 13.6 | .24|
| Preadmission meds, % | | | |
| Statins | 66.7 | 52.3 | .21|
| ARB/ARB | 66.7 | 22.7 | .0001|
| Glucose metrics | | | |
| Mean BG, mg/dL | 141 (111-163) | 133 (115-147) | .23|
| Coefficient of variation, % | 31.4 (23.1-37.2) | 27.7 (20.9-33.6) | .34|
| Hypoglycemia < 70 mg/dL<sup>a</sup> | 33.3 | 40.9 | .50|
| SC insulin received in ICU<sup>a</sup> | 72.2 | 72.7 | ≥ .999|
| IV insulin received in ICU<sup>a</sup> | 57.6 | 45.4 | .29|
| HbA<sub>1c</sub>, % | 10.5 (7.7-12.1) | 8.9 (7.9-10.9) | .14|
| GR | 0.58 (0.34-0.64) | 0.61 (0.54-0.66) | .29|
| Clinical | | | |
| Mechanical ventilation, % | 42.4 | 38.6 | .74|
| ICU LOS, d | 2.6 (1.2-5.8) | 1.6 (0.9-4.0) | .18|
| APACHE IV predicted mortality, % | 19.0 (21.9) | 22.9 (28.0) | .51|
| Mortality, % | 15.2 | 18.2 | .73|
| Observed:Expected mortality ratio | 0.80 | 0.79 | .91|
| GR 0.7-<0.9 | | | |
| No. | 108 | 127 | | |
| Age, y | 71 (61-82) | 69 (57-80) | .12|
| Male, % | 48.1 | 59.1 | .0924|
| BMI | 29.9 (25.3-34.4) | 28.4 (25.0-34.6) | .39|
| eGFR, % of patients | | | |
| > 60 | 48.1 | 59.4 | .0838|
| 40-59 | 19.4 | 16.4 | .55|
| 20-39 | 15.7 | 17.2 | .76|
| < 20 | 16.7 | 7.0 | .0203|
| Comorbidities (% of patients) | | | |
| Current smoker | 11.1 | 7.1 | .29|
| Past smoker | 31.5 | 37.8 | .31|

(continued)
Table 5. Continued

| Comorbidity                  | GR 0.81-0.9 | GR 0.9-<1.1 | P     |
|------------------------------|-------------|-------------|-------|
| DM                           | undiagDM    |             |       |
| Hypertension                 | 83.3        | 71.7        | .0355 |
| Hyperlipidemia               | 83.3        | 73.2        | .0637 |
| CAD                          | 64.8        | 30.7        | <.0001|
| Cerebrovascular disease      | 25.9        | 23.6        | .68   |
| Peripheral vascular disease  | 29.6        | 11.8        | .0007 |
| Preadmission meds, %         |             |             |       |
| Statins                      | 72.2        | 49.6        | .0004 |
| ARB/ARB                      | 49.1        | 30.7        | .0041 |
| Glucose metrics              |             |             |       |
| Mean BG, mg/dL               | 138 (123-154) | 126 (118-143) | .0042 |
| Coefficient of variation, %  | 25.7 (20.0-31.9) | 20.3 (15.5-28.9) | .0002 |
| Hypoglycemia < 70 mg/dL     | 30.6        | 16.5        | .0106 |
| SC insulin received in ICU   | 84.3        | 76.4        | .13   |
| IV insulin received in ICU   | 43.5        | 21.3        | .0003 |
| HbA1c, %                     | 7.2 (6.8-8.1) | 6.9 (6.6-7.8) | .0026 |
| GR                           | 0.81 (0.76-0.86) | 0.81 (0.76-0.85) | .73   |
| Clinical                     |             |             |       |
| Mechanical ventilation, %    | 48.2        | 49.5        | .79   |
| ICU LOS, d                   | 1.8 (1.1-3.9) | 2.1 (1.3-4.1) | .40   |
| APACHE IV predicted mortality, % | 21.9 (24.3) | 22.6 (23.6) | .84   |
| Mortality, %                 | 13.9        | 14.2        | .95   |
| Observed:Expected mortality ratio | 0.63 | 0.63 | ≥.999 |
| eGFR, % of patients          |             |             |       |
| > 60                         | 45.2        | 60.2        | .0301 |
| 40-59                        | 24.3        | 19.4        | .39   |
| 20-39                        | 14.8        | 12.2        | .58   |
| < 20                         | 15.7        | 8.8         | .13   |
| Comorbidities, % of patients |             |             |       |
| Current smoker               | 7.9         | 14.4        | .13   |
| Past smoker                  | 41.2        | 33.0        | .22   |
| Hypertension                 | 83.3        | 63.9        | .0013 |
| Hyperlipidemia               | 74.6        | 49.4        | .0012 |
| CAD                          | 50.9        | 34.0        | .0137 |
| Cerebrovascular disease      | 25.4        | 28.9        | .57   |
| Peripheral vascular disease  | 29.8        | 14.4        | .0079 |
| Preadmission meds, %         |             |             |       |
| Statins                      | 64.0        | 53.6        | .13   |
| ARB/ARB                      | 50.0        | 30.9        | .0051 |
| Glucose metrics              |             |             |       |
| Mean BG, mg/dL               | 155 (144-169) | 148 (136-158) | .0005 |
| Coefficient of variation, %  | 27.5 (20.8-35.0) | 21.1 (16.1-26.9) | <.0001|
| Hypoglycemia < 70 mg/dL     | 21.1        | 12.4        | .0952 |
### Table 5. Continued

| GR<0.7 | DM | undiagDM | P  |
|--------|----|-----------|----|
| SC insulin received in ICU* | 99.1 | 91.8 | .50 |
| IV insulin received in ICU* | 56.1 | 25.8 | <.0001 |
| HbA1c, % | 7.0 (6.7-7.5) | 6.7 (6.5-7.2) | .0003 |
| GR | 0.98 (0.93-1.02) | 0.97 (0.94-1.01) | .61 |

**Clinical**

- Mechanical ventilation, %: 42.1 vs. 47.4, P=.44
- ICU LOS, d: 2.5 (1.2-4.3) vs. 1.9 (1.0-5.6), P=.60
- APACHE IV predicted mortality, %: 25.0 (25.1) vs. 21.7 (24.1), P=.32
- Mortality, %: 14.0 vs. 13.4, P=.90
- Observed:Expected mortality ratio: 0.56 vs. 0.62, P=.38

| GR ≥ 1.1 | DM | undiagDM | P  |
|----------|----|-----------|----|
| No. | 39 | 26 |    |
| Age, y | 75 (65-82) | 71 (61-85) | .76 |
| Male, % | 56.4 | 69.2 | .30 |
| BMI | 28.2 (26.2-32.4) | 25.4 (24.4-35.2) | .23 |
| eGFR, % of patients |        |        |    |
| > 60 | 46.2 | 57.7 | .37 |
| 40-59 | 25.6 | 26.9 | .91 |
| 20-39 | 7.7 | 0.0 | .15 |
| < 20 | 20.5 | 15.4 | .61 |
| Comorbidities, % of patients |        |        |    |
| Current smoker | 5.1 | 7.7 | .67 |
| Past smoker | 56.4 | 34.6 | .0872 |
| Hypertension | 82.1 | 76.9 | .61 |
| Hyperlipidemia | 72.0 | 65.4 | .57 |
| CAD | 48.2 | 42.3 | .64 |
| Cerebrovascular disease | 15.4 | 23.1 | .44 |
| Peripheral vascular disease | 30.8 | 7.7 | .0277 |
| Preadmission meds, % |        |        |    |
| Statins | 72.0 | 57.7 | .24 |
| ARB/ARB | 43.6 | 34.6 | .47 |
| Glucose metrics |        |        |    |
| Mean BG, mg/dL | 181 (170-211) | 170 (160-187) | .11 |
| Coefficient of variation, % | 28.2 (21.7-38.6) | 24.7 (18.1-34.1) | .14 |
| Hypoglycemia < 70 mg/dL* | 5.1 | 7.7 | .67 |
| SC insulin received in ICU* | 89.7 | 84.6 | .54 |
| IV insulin received in ICU* | 59.0 | 46.2 | .31 |
| HbA1c, % | 7.1 (6.6-7.3) | 6.7 (6.6-6.9) | .13 |
| GR | 1.21 (1.14-1.33) | 1.19 (1.12-1.27) | .49 |

**Clinical**

- Mechanical ventilation, %: 19.6 vs. 22.2
- ICU LOS, d: 1.2 (0.8=2.5) vs. 1.5 (1.1-2.8), P=.39
- APACHE IV predicted mortality, %: 19.9 (23.5) vs. 32.5 (35.2), P=.0867
- Mortality, %: 10.3 vs. 38.5, P=.0072
- Observed:Expected mortality ratio: 0.52 vs. 1.18, <.0001

Abbreviations: ACE/ARB, angiotensin-converting enzyme/angiotensin receptor blockade; APACHE, Acute Physiology and Chronic Health Evaluation; BG, blood glucose; BMI, body mass index; CAD, coronary artery disease; DM, diabetes patients; eGFR, estimated glomerular filtration rate; GR, glycemic ration; HbA1c, glycated hemoglobin A1c; ICU, intensive care unit; IV, intravenous; LOS, length of stay; SC, subcutaneous; undiagDM, previously undiagnosed diabetes patients. Percentage of patients.
whereas the opposite was seen with DM patients. Here, it is possible that this finding reflects the fact that patients previously diagnosed with diabetes were exposed to higher circulating insulin levels before admission, owing to treatment either with insulin itself (48.3%) or with drugs such as sulfonylureas (21.5%) that increase insulin secretion. At issue is whether such treatments induce stable physiological adaptations that are protective against hyperglycemia in the ICU.

The Diabetes Control and Complications Trial (DCCT) (1982-1993) compared intensive insulin therapy (INT) aimed at achieving levels of glycemia close to the nondiabetic range with conventional insulin therapy (CON) [30]. Following these findings, the Epidemiology of Diabetes Interventions and Complications (EDIC) study was initiated to examine the long-term effects of the original DCCT interventions on diabetic complications [31]. During EDIC, both INT and CON groups had identical HbA1c levels of approximately 8% at follow-up. Even though the HbA1c level was now comparably elevated between groups, the beneficial effects of previous lower HbA1c in the INT group persisted as if there had been no deterioration in their HbA1c. This outcome was shown to reflect stably altered DNA methylation patterns that occurred during the DCCT [32].

The markedly higher mortality risk seen in undiagDM patients with high mean ICU BG could also involve other factors that raise sensitivity to ICU hyperglycemia. For example, the lower preadmission use of statins in undiagDM group could have contributed, since this has been associated with reduced ICU mortality [33]. It is also possible that patients in the undiagDM group were less likely to have received regular medical attention or were burdened with unrecognized disease contributing to impaired response to physiologic stress.

**Strengths and Limitations**

Strengths of this investigation include its rich data set, including comorbidities, severity of illness, and detailed glucose metrics. The database was maintained and updated prospectively, and the accuracy of the designation of DM and undiagDM was validated by detailed review of individual patient records. In addition, the case-control methodology, with 100% matching of patients without DM and the relative tolerance to hyperglycemia (GR ≥ 1.1). These data suggest that the tolerance to hyperglycemia among patients with established DM—the attenuation of an association of hyperglycemia with mortality in the critically ill—as described in prior observational studies [3–8], had not yet developed in this cohort of undiagDM.

In summary, glucose control in the critically ill is abnormal in undiagDM but not as abnormal as in DM and, furthermore, undiagDM retain sensitivity to the deleterious effect of hyperglycemia, an association not seen in DM. These data place the undiagDM cohort on a spectrum between patients without DM and those with established DM. These data strengthen the association of hyperglycemia with mortality in patients without DM and the relative tolerance to hyperglycemia among those with established DM, especially those with high HbA1c. Finally, these data provide impetus to the need to perform well-designed randomized trials to test the paradigm of individualized glucose control in the critically ill.

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**Author Contributions**

J.K. wrote the first draft of the manuscript and was responsible for the designation of the methodology. All authors were responsible for the critical revision of the article for important intellectual content. J.K., Y.W., and J.B. were

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This inference sheds light on the observed differences in glucose control. While both groups were treated with the same ICU BG management protocols, undiagDM had lower mean BG, lower CV, and less frequent hypoglycemia than did DM patients. Previous literature has documented similar differences in glucose metrics when comparing cohorts of ICU patients with and without DM, as well as the relationship of higher HbA1c with greater derangements in ICU glucose control [9–18].

Finally, our data demonstrate important differences in the relationship of ICU glycemia to mortality for the 2 groups. We used the GR, the quotient of mean ICU BG and estimated preadmission glycemia [18], to reflect the degree of divergence of ICU glycemia from baseline glycemia. The undiagDM cohort had higher risk-adjusted mortality than did the DM cohort. This is attributable to the much higher mortality associated with GR greater than or equal to 1.1 in undiagDM than in DM; for GR values less than 1.1, both absolute and risk-adjusted mortality were similar (see Fig. 2A and 2B, respectively) comparing DM and undiagDM.

Elevated GR reflects hyperglycemia relative to preadmission glycemia. The undiagDM, therefore, demonstrated the same association of elevated mean ICU BG with mortality that has been documented in numerous observational studies of patients without DM [3–8]. In contrast, both absolute and risk-adjusted mortality were numerically lower in the DM cohort with relative hyperglycemia (GR ≥ 1.1). These data suggest that the tolerance to hyperglycemia among patients with established DM—the attenuation of an association of hyperglycemia with mortality in the critically ill—as described in prior observational studies [3–8], had not yet developed in this cohort of undiagDM.

Clinical Implications

These data shed light on the natural history of DM, glucose metrics during critical illness in these patients, and the relationship of ICU glycemia to mortality.

The undiagDM cohort may have sustained a shorter duration of DM before ICU admission compared to the matched DM group, as demonstrated by their significantly lower burden of important comorbidities. Therefore, this group of patients can be placed on the spectrum of impaired glucose regulation between patients without DM and those with established disease.

**Clinical Implications**

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In summary, glucose control in the critically ill is abnormal in undiagDM but not as abnormal as in DM and, furthermore, undiagDM retain sensitivity to the deleterious effect of hyperglycemia, an association not seen in DM. These data place the undiagDM cohort on a spectrum between patients without DM and those with established DM. These data strengthen the association of hyperglycemia with mortality in patients without DM and the relative tolerance to hyperglycemia among those with established DM, especially those with high HbA1c. Finally, these data provide impetus to the need to perform well-designed randomized trials to test the paradigm of individualized glucose control in the critically ill.

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**Author Contributions**

J.K. wrote the first draft of the manuscript and was responsible for the designation of the methodology. All authors were responsible for the critical revision of the article for important intellectual content. J.K., Y.W., and J.B. were
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Data Availability
The data that support the findings of this study are not publicly available. However, the corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Clinical Trials Information
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References
1. Wang L, Li X, Wang Z, et al. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999-2018. JAMA. 2021;326(8):704-716.
2. Dhattariya K, Corsino L, Umpierrez GE. Management of diabetes and hyperglycemia in hospitalized patients [updated December 30, 2020]. In: Feingold KR, Anawalt B, Boyce A, et al, eds. Endotext. MDText.com Inc; 2000. Accessed June 29, 2022. https://www.ncbi.nlm.nih.gov/books/NBK279093/
3. Krinsley JS. Glycemic control, diabetic status and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years of experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg. 2006;18(4):317-325.
4. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med. 2008;36(8):2249-2255.
5. Bagshaw S, Egi M, George C, Bellomo R. Early blood glucose control and mortality in critically ill patients in Australia. Crit Care Med. 2009;37(2):463-470.
6. Falciglia M, Freyberg RW, Almenoff PL, D’Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37(12):3001-3009.
7. Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relationship of the 3 domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care. 2013;17(2):R37.
8. Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM, et al. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. Crit Care. 2013;17(2):R52.
9. Egi M, Bellomo R, Stachowski E, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med. 2011;39(1):105-111.
10. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycemia in the critically ill and the interaction of chronic and acute glycemia with mortality. Int Care Med. 2014;40(7):973-980.
11. Roberts G, Quinn SJ, Valentine N, et al. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. J Clin Endo Met. 2015;100(12):4490-4497.
12. Liao W, Wang JC, Chang WC, et al. Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. Medicine (Baltimore). 2015;94(36):e1525.
13. Krinsley JS, Rule P, Pappy L, et al. The interaction of acute and chronic glycemia on the relationship of hyperglycemia, hypoglycemia and glucose variability to mortality in the critically ill. Crit Care Med. 2020;48(12):1744-1751.
14. Kwan TN, Zwakman-Hessels L, Marhoon N, et al. Relative hyperglycemia in diabetic patients with critical illness. Crit Care Med. 2020;48(3):E233-E240.
15. Lec TF, Drake SM, Roberts GW, et al. Relative hyperglycemia is an independent determinant of in-hospital mortality in patients with critical illness. Crit Care Med. 2020;48(2):e115-e122.
16. Krinsley JS, Rule PR, Brownlee M, et al. Acute and chronic glucose control in critically ill patients with diabetes: impact of prior insulin treatment. J Diab Sci Tech. 2012;6(6):1483-1495.
17. Krinsley JS, Rule PR, Brownlee M, et al. Relative hypoglycemia and lower hemoglobin A1c-adjusted time in band (HA-TlB) are strongly associated with increased mortality in critically ill patients. Crit Care Med. 2022;50(8):e664-e673.
18. Roberts G, Krinsley JF, Preiser JC, et al. The glycemic ratio is strongly and independently associated with mortality in the critically ill. J Diabetes Technol. Published online September 12, 2022. doi:10.1177/19322968221124114
19. Greci LS, Kailasam M, Malkani S, et al. Utility of HbA1c levels for diabetes case finding in hospitalized patients with hyperglycemia. Diab Care. 2003;26(4):1064-1068.
20. Wexler DJ, Nathan DM, Grant RW, Regan S, Van Leuven AL, Cagliero E. Prevalence of elevated hemoglobin A1c among patients admitted to the hospital without a diagnosis of diabetes. J Clin Endocrinol Metab. 2008;93(11):4238-4244.
21. Carpenter DL, Gregg SR, Xu K, Buchman TG, Coopersmith CM. Prevalence, and impact of unknown diabetes in the ICU. Crit Care Med. 2013;41(12):e341-e350.
22. Mazurek JA, Hallipern SM, Goring T, Nordin C. Prevalence of hemoglobin A1c greater than 6.5% and 7.0% among hospitalized patients without known diagnosis of diabetes at an urban inner city hospital. J Clin Endocrinol Metab. 2010;95(3):1344-1348.
23. Du YT, Kar P, Abdelhamid YA, Horowitz M, Deane AM. Glycated haemoglobin is increased in critically ill patients with stress hyperglycaemia: implications for risk of diabetes in survivors of critical illness. Diab Res Clin Pract. 2018;135:73-75.
24. Hoang QN, Pisani MA, Inzucchi S, Hu B, Honiden S. The prevalence of undiagnosed diabetes mellitus and the association of baseline glycemic control on mortality in the intensive care unit: a prospective observational study. J Crit Care. 2014;29(6):1052-1056.
25. Krinsley JS, Preiser JC, Hirsch IB. Safety and efficacy of personalized glycemic control in critically ill patients: a 2-year before and after interventional trial. Endocr Pract. 2017;23(3):318-330.
26. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today’s critically ill patients. Crit Care Med. 2006;34(5):1297-1310.
27. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. Wiley; 1981.
28. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ: A1c-Derived Average Glucose Study Group. Translating the A1C
29. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87(3):978-982.

30. Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care*. 1987;10(1):1-19.

31. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in Type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care*. 2016;39(5):686-693.

32. Chen Z, Miao F, Braffett BH, et al. DNA Methylation mediates development of HbA1c-associated complications in type 1 diabetes. *Nat Metab*. 2020;2(8):744-762.

33. Dobesh PP, Klepser DG, McGuire TR, Morgan CW, Olsen KM. Reduction in mortality associated with statin therapy in patients with severe sepsis. *Pharmacotherapy*. 2009;29(6):621-630.

34. Rubinow KB, Hirsch IB. Reexamining metrics for glucose control. *JAMA*. 2011;305(11):1132-1133.