# Acute-to-Chronic Glycemic Ratio as a Predictor of COVID-19 Severity and Mortality

*Diabetes Care 2022;45:255–258 | https://doi.org/10.2337/dc21-1321*

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## OBJECTIVE

**To evaluate the association between acute-to-chronic (A/C) glycemic ratio and mortality and severity outcomes for patients with type 2 diabetes (T2D) hospitalized with coronavirus disease 2019 (COVID-19).**

## RESEARCH DESIGN AND METHODS

**A total of 91 patients were included. We measured glycemia at admission and estimated the average chronic glucose levels to calculate the A/C glycemic ratio. The primary outcome was a composite of in-hospital mortality, intensive care unit admission, and mechanical ventilation.**

## RESULTS

**Thirty-five patients had a primary outcome event, presenting a significant association with the A/C glycemic ratio (hazard ratio [HR] 1.57 [95% CI 1.14–2.15], $P = 0.005$). In comparisons with the 2nd tertile, the 3rd tertile of the A/C glycemic ratio was associated with the primary outcome (HR 3.39 [95% CI 1.31–8.75], $P = 0.012$). In the multivariate analysis, after additional adjustment for age, sex, comorbidities, inflammatory markers, and corticosteroid therapy, the association for the 3rd tertile (HR 3.96 [95% CI 1.35–11.59], $P = 0.012$) remained significant.**

## CONCLUSIONS

**In patients with T2D hospitalized with COVID-19, the imbalance between acute glycemia at admission and chronic metabolic control is associated with worse prognosis.**

The coronavirus disease 2019 (COVID-19) fatality rate has been estimated at 0.5–1.0% (1–3). High glucose levels at admission and underlying diabetes have been considered risk factors for greater severity and worse outcomes (4). Nevertheless, data for evaluating the impact of chronic glycemic control remain scarce (5,6). It has been previously demonstrated that the acute-to-chronic (A/C) glycemic ratio is associated with poor prognosis in cardiovascular disease (7). Thus, our aim was to assess whether the A/C glycemic ratio was associated with mortality and severity outcomes in patients with type 2 diabetes (T2D) hospitalized with COVID-19.

## RESEARCH DESIGN AND METHODS

An observational cohort study was conducted at Hospital del Mar. The study procedures have previously been described (8). The Hospital del Mar Institutional Ethics Committee approved the study and, due to the study nature, waived the informed

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*Received 24 June 2021 and accepted 27 October 2021*

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*This article is part of a special article collection available at https://diabetesjournals.org/journals/collection/52/Diabetes-and-COVID-19.*

consent need (CEIm-2020/9352). All patients with T2D admitted with COVID-19 between March and April 2020 were included. Diabetes was defined on the basis of self-reported physician diagnosis, hypoglycemic medication use, or $HbA_{1c}$ ≥6.5% (≥48 mmol/mol). The average chronic glucose levels and the A/C glycemic ratio were calculated according to the following validated formulas (7):

Estimated chronic glucose levels (mg/dL) = (28.7 × $HbA_{1c}$) − 46.7

A/C glycemic ratio = glucose at admission (mg/dL) / estimated chronic glucose (mg/dL)

Patients were stratified according to A/C glycemic ratio tertiles. The primary outcome was a composite of in-hospital mortality, intensive care unit (ICU) admission, and mechanical ventilation (MV). The secondary outcomes were in-hospital mortality, ICU admission, MV, acute respiratory distress syndrome (ARDS), and hospital stay length.

### Statistical Analysis

Data were tested for normality (Shapiro-Wilk) and are presented as percentage, mean (SD), or median (interquartile range [IQR]). The association between the A/C glycemic ratio and the primary outcome was assessed with unadjusted/adjusted Cox proportional hazards models. The 2nd tertile was used as the reference group. Results are expressed as hazard ratio (HR) (95% CI). The association between secondary end points and glucose at admission, estimated chronic glucose levels, A/C glycemic ratio, and $HbA_{1c}$ tertiles was assessed with logistic regression. Two-tailed *P* values <0.05 were considered statistically significant. The calculations were made with STATA v.16.1 for Mac (StataCorp, College Station, TX).

## RESULTS

Baseline characteristics are shown in Table 1. Over a median observation period of 12 days (IQR 7–23), 35 patients (38.9%) presented a primary event: 11 (35.5%) in the 1st, 6 (20.7%) in the 2nd, and 18 (60.0%) in the 3rd tertile. Overall, there was a significant association between the A/C glycemic ratio and the primary outcome (HR 1.57 [95% CI 1.14–2.15], $P = 0.005$). When the results were analyzed according to A/C glycemic ratio tertiles, compared with the 2nd, the 3rd tertile was associated with the primary outcome (HR 3.39 [95% CI 1.31–8.75], $P = 0.012$) with no difference for the 1st tertile (HR 2.16 [95% CI 0.80–5.86], $P = 0.130$), with a comprehensive Kaplan-Meier log-rank of 7.37 ($P = 0.025$). After adjustment for age, sex, comorbidities, inflammatory markers, and corticosteroid therapy, the 3rd tertile remained an independent predictor (HR 3.96 [95% CI 1.35–11.59], $P = 0.012$). By contrast, no association was found between glucose at admission, estimated chronic glucose levels, $HbA_{1c}$ tertiles, and the primary outcome.

Regarding the secondary outcomes, there was also a significant association between the A/C glycemic ratio and in-hospital mortality (HR 2.01 [95% CI 1.18–3.45], $P = 0.011$). When the results were analyzed according to tertiles, a U-shaped curve association was found. In comparisons with the 2nd tertile, the mortality rate in the 1st tertile was higher (HR 4.88 [95% CI 1.03–23.05], $P = 0.045$) but that in the 3rd tertile was only marginally so (HR 4.26 [95% CI 0.92–19.79], $P = 0.064$), with a comprehensive Kaplan-Meier log-rank of 5.09 ($P = 0.079$).

There was no significant association between A/C glycemic ratio and the other secondary outcomes. However, and although there was no significance in the overall results, when the results were analyzed across tertiles, a significant association emerged for those patients in the 3rd tertile of glucose at admission, having higher risk of ICU admission (OR 9.4 [95% CI 1.9–45.2], $P = 0.005$), MV (OR 3.9 [95% CI 1.2–12.3], $P = 0.020$), and ARDS (OR 3.8 [95% CI 1.4–10.2], $P = 0.008$), with a longer hospital stay ($\beta = 0.280$, $P = 0.013$), in comparisons with the 1st tertile.

## CONCLUSIONS

The main finding of the current study is that in patients with T2D hospitalized with COVID-19, the A/C glycemic ratio is associated with an increased risk of in-hospital mortality, ICU admission, and MV. Additionally, higher in-hospital mortality rates are associated with both the lowest and highest A/C glycemic ratio tertiles, producing a U-shaped mortality curve. However, hyperglycemia at admission is associated with poor outcomes but not with in-hospital mortality.

Studies conducted in patients with sepsis have shown that previous diabetes or hyperglycemia at admission are common risk factors for poor prognosis (9,10). A recent meta-analysis showed that hyperglycemia at admission independently predicted poor prognosis in COVID-19 (11). By contrast, in our study, glucose at admission was associated with poor outcomes but not with in-hospital mortality. Previous studies in critically ill patients have shown that, for equal glucose levels at admission, those without diabetes had a poorer prognosis than those with diabetes (12), suggesting that the magnitude of the acute glycemic rise from chronic levels, rather than the glycemic level per se, could be detrimental. Thus, some authors have suggested that the A/C glycemic ratio could better identify true stress hyperglycemia than glucose at admission (7). To our knowledge, our study is the first evaluating the potential role of the A/C glycemic ratio as a prognostic factor in patients hospitalized with COVID-19.

In patients with acute myocardial infarction, the A/C glycemic ratio was associated with worse outcomes, indicating improved prediction capacity with glycemia at admission and $HbA_{1c}$ (7). Accordingly, we observed that patients in the highest A/C glycemic ratio tertile (with acute glycemic levels 22% higher than the expected) had an increased risk of in-hospital mortality, ICU admission, and MV. Nevertheless, no association was found between glucose at admission or $HbA_{1c}$ and the primary outcome. Thus, our results would suggest that A/C glycemic ratio would achieve a better prognostic value than each component alone.

Moreover, we observed that higher in-hospital mortality rates were associated with both the lowest and highest A/C glycemic ratio tertiles, producing a U-shaped mortality curve. There was a higher in-hospital mortality rate for patients in the 1st tertile (with glycemia at admission 18% lower than the expected). In that sense, it is important to highlight that most patients in the 1st tertile were admitted in a state of euglycemia, but, according to the A/C glycemic ratio, they presented a "relative hypoglycemia." The

**Table 1—Baseline characteristics and outcomes of the subjects according to A/C glycemic ratio tertiles**

| | Whole population | A/C glycemic ratio tertile | | | *P* for trend |
|---|---|---|---|---|---|
| | | 1st tertile (≤0.82) | 2nd tertile (0.83–1.21) | 3rd tertile (≥1.22) | |
| *n* | 91 | 31 | 30 | 30 | |
| Age (years) | 75 (63–85) | 75 (62–85) | 71 (61–82) | 76 (66–85) | 0.639 |
| Female/male sex | 45 (49.5)/46 (50.5) | 14 (45.1)/17 (54.8) | 14 (46.7)/16 (53.3) | 17 (56.7/13 (43.3) | 0.623 |
| Active smokers | 7 (7.7) | 4 (12.9) | 2 (6.7) | 1 (3.3) | 0.494 |
| Body weight (kg) | 75.0 (65.0–85.0) | 74.5 (65.0–84.0) | 80.0 (67.0–94.0) | 70.0 (61.0–85.0) | 0.337 |
| BMI (kg/m$^2$) | 28.7 (25.1–31.3) | 28.5 (25.1–34.4) | 29.1 (25.9–31.4) | 26.3 (23.5–31.0) | 0.389 |
| Comorbidities | | | | | |
| Obesity | 25 (28.7) | 7 (23.3) | 11 (37.9) | 7 (25.0) | 0.443 |
| Hypertension | 77 (84.6) | 26 (83.9) | 27 (90.0) | 24 (80.0) | 0.589 |
| Dyslipidemia | 50 (54.9) | 17 (54.8) | 19 (63.3) | 14 (46.7) | 0.431 |
| Cardiovascular disease | 29 (31.9) | 8 (25.8) | 12 (40.0) | 9 (30.0) | 0.476 |
| Chronic respiratory disease | 11 (12.1) | 3 (9.7) | 6 (20.0) | 2 (6.7) | 0.273 |
| Chronic kidney disease | 7 (7.7) | 2 (6.4) | 3 (10.0) | 2 (6.7) | 0.895 |
| Laboratory parameters | | | | | |
| Glucose at admission (mmol/L) | 8.3 (6.4–12.0) | 6.1 (5.2–7.9) | 8.1 (6.7–9.9)* | 14.7 (11.8–19.1)†‡ | <0.001 |
| Estimated chronic glucose (mmol/L) | 8.6 (7.8–10.8) | 9.8 (8.6–10.9) | 8.2 (7.3–9.5)* | 8.4 (7.6–10.9) | 0.032 |
| $HbA_{1c}$ (%) | 7.0 (6.5–8.4) | 7.8 (7.0–8.5) | 6.8 (6.2–7.6)* | 6.9 (6.4–8.5) | 0.031 |
| $HbA_{1c}$ (mmol/mol) | 53 (48–68) | 62 (53–69) | 51 (44–60)* | 52 (46–69) | 0.031 |
| C-reactive protein (nmol/L) | 752.4 (381.0–1561.9) | 514.3 (142.6–809.5) | 847.6 (523.8–1,504.8)* | 1,514.3 (419.0–2,485.7)† | 0.002 |
| Ferritin (pmol/L) | 1,519.0 (732.5–2,709.9) | 1,004.4 (521.3–1,901.0) | 1,505.5 (912.3–2,608.8) | 2,309.9 (1,240.3–3,557.0) | 0.165 |
| Interleukin-6 (UI/L) | 531.8 (171.0–953.3) | 523.4 (353.3–962.6) | 394.4 (170.1–615.9) | 775.7 (200.0–1,231.8) | 0.227 |
| D-dimer (UI/L) | 700 (450–1,490) | 620 (350–970) | 860 (510–1,555)* | 865 (500–2,710)† | 0.045 |
| Severity parameters | | | | | |
| MEWS | 2 (1–3) | 2 (1–3) | 2 (1 3) | 2 (2–3) | 0.637 |
| CURB-65 | 2 (1–2) | 2 (1–2) | 1 (1–2) | 2 (2–3)†‡ | 0.021 |
| $PaO_2$-to-$FiO_2$ ratio | 200 (99–300) | 203 (128–308) | 243 (100–307) | 154 (91–271) | 0.306 |
| Outcomes | | | | | |
| Primary outcome event | 35 (38.9) | 11 (35.5) | 6 (20.7) | 18 (60.0)‡ | 0.007 |
| Length of stay (days) | 12.0 (7.0–21.9) | 8.5 (5.0–15.0) | 13.5 (9.0–22.5) | 16.9 (8.0–25.5) | 0.359 |
| ARDS | 34 (38.2) | 8 (26.7) | 11 (36.7) | 15 (51.7) | 0.185 |
| Invasive MV | 17 (19.3) | 5 (16.7) | 4 (13.8) | 8 (27.6) | 0.438 |
| ICU admission | 18 (19.8) | 3 (9.7) | 5 (16.7) | 10 (33.3) | 0.073 |
| Mortality | 19 (20.9) | 8 (25.8) | 2 (6.7) | 9 (30.0) | 0.059 |

Data are given as median (IQR) or *n* (%) unless otherwise indicated. CURB-65, confusion, urea >7 mmol/L, respiratory rate ≥30/min, low blood pressure ≤90/60 mmHg, and age 65 years; $FiO_2$, fraction of inspired oxygen; MEWS, Modified Early Warning Score; $PaO_2$, arterial partial pressure of oxygen. *$P < 0.05$ for 2nd tertile compared with 1st tertile; †$P < 0.05$ for 3rd tertile compared with 1st tertile; ‡$P < 0.05$ for 3rd tertile compared with 2nd tertile.

possible explanations are a partial ACTH deficiency (up to 25% of critically ill patients) (13), impairment in sympathetic nervous system response, the induction of hypotension, vasodilatation, and nitric oxide (NO) release (12).

Our study has several limitations. Conclusions regarding causality cannot be drawn due to the observational study design, without a control group. The study was conducted during the first wave, and new management strategies are now in force, which may have influenced outcomes. This is a single-center study with a limited sample size. Finally, data on in-hospital glucose management were not collected, preventing the evaluation of its potential impact. The study also has important strengths. All patients were attended in the COVID-19 unit under the same guidelines, with robust clinical protocols that made the data management uniform.

In conclusion, in subjects with T2D, an imbalance between glycemia at admission and chronic metabolic control might be detrimental, having better prognostic value than each component alone. Although further studies with a large sample size are needed, our findings

suggest the potential role of routine $HbA_{1c}$ determination (added to glucose at admission) in subjects with T2D hospitalized with COVID-19 for correct assessment of their prognosis and, possibly, modification of glucose management.

**Acknowledgments.** The authors particularly acknowledge all the individuals enrolled in this study and their physicians for their participation and Kenneth McCreath for editing the English version of the manuscript.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** J.R. researched data and wrote the manuscript. G.L. researched data, contributed to the study concept and design, analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. R.G. researched data, contributed to the discussion, and reviewed and edited the manuscript. E.C. researched data. S.B. performed statistical analysis. D.B. researched data. I.L.-M. researched data. H.N. researched data. N.F. researched data. M.J.C. researched data. D.M. contributed to the discussion and reviewed and edited the manuscript. J.A.F.-L.R. contributed to the discussion and reviewed and edited the manuscript. J.-J.C. researched data, contributed to the study concept and design, analyzed and interpreted data, wrote the manuscript, and supervised the study. R.G. and J.-J.C. 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.

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