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## Review Article

## Effect of COVID 19 pneumonia on hyperglycemia: Is it different from non COVID pneumonia?

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## ABSTRACT

**Background and aims:** Glycemic control in critical illness has been linked to outcomes. We sought to investigate if COVID pneumonia was causing disrupted glycemic control compared to historically similar diseases.

**Methods:** At Intermountain Healthcare, a 23-hospital healthcare system in the intermountain west, we performed a multicenter, retrospective cohort observational study. We compared 13,268 hospitalized patients with COVID pneumonia to 6673 patients with non-COVID-pneumonia.

**Results:** Patients with COVID-19 were younger had fewer comorbidities, had lower mortality and greater length of hospital stay. Our regression models demonstrated that daily insulin dose, indexed for weight, was associated with COVID-19, age, diabetic status, HgbA1c, admission SOFA, ICU length of stay and receipt of corticosteroids. There was significant interaction between a diagnosis of diabetes and having COVID-19. Time in range for our IV insulin protocol was not correlated with having COVID after adjustment. It was correlated with ICU length of stay, diabetic control (HgbA1C) and prior history of diabetes. Among patients with subcutaneous (SQ) insulin only percent of glucose checks in range was correlated with diabetic status, having Covid-19, HgbA1c, total steroids given and Elixhauser comorbidity score even when controlled for other factors.

**Conclusions:** Hospitalized patients with COVID-19 pneumonia who receive insulin for glycemic control require both more SQ and IV insulin than the non-COVID-19 pneumonia counterparts. Patients with COVID-19 who received SQ insulin only had a lower percent of glucose checks in range.

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## 1. Introduction

Glycemic control remains key component of critical care management. The novel coronavirus disease 2019 (COVID-19) appears to have greater disease burden among individuals with diabetes [1,2]. In some observations, patients with COVID-19 present with higher-than-expected hyperglycemia, including those without pre-existing diabetes [3]. Critically ill patients with COVID-19 may present with reduced insulin sensitivity, impaired glycemic homeostasis, and higher glycemic variability. While there is a mechanistic rationale for COVID-19 causing hyperglycemia, these abnormalities are also observed in critically ill patients without

COVID-19. It is unclear how much of the glycemic variability or insulin insensitivity reported in critically ill patients with COVID-19 is unique to COVID-19, and how much is a manifestation of critical illness.

One of the key domains of glucose control in the intensive care unit (ICU) is time in range (TIR), which is the percent of time a patient maintains a blood glucose between a goal target range (70 and 140 mg/dL in some protocols). Higher TIR is associated with reduced mortality in critically ill patients, more so among non-diabetic patients and in patients with good antecedent blood glucose control [4,5]. TIR is also a descriptor used to measure glucose control protocols in the ICU.

Intermountain Healthcare, the largest healthcare provider in the Intermountain West, developed and implemented a point-of-care electronic protocol for IV insulin (eProtocol-Insulin). eProtocol-insulin is employed routinely in hyperglycemic patients with high

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clinician compliance with protocol recommendations across multiple Intermountain healthcare ICUs. All hyperglycemic patients treated with IV insulin (both with and without COVID-19) are treated using eProtocol-insulin, allowing for comparisons between cohorts of patients. All transitions of insulin from IV to SQ are managed by the protocol. We sought to compare patients with COVID-19 pneumonia to patients with non-COVID-19 pneumonia and assess glycemic responses to eProtocol-insulin and standard subcutaneous (SQ) insulin sliding scale. We hypothesized that patients with COVID-19 pneumonia would respond to insulin in a similar manner to patients with non-covid-19 pneumonia.

## 2. Materials and methods

This is a multicenter, retrospective cohort observational study. We utilized the complete Electronic Database Warehouse of Intermountain Healthcare, a 23-hospital system located in 5 states of the Intermountain West. We compared all patients admitted with a lab confirmed diagnosis of COVID-19 from January 1, 2020 through July 31, 2021 to a cohort of patients with pneumonia who were obtained using previous published methodology from January 1, 2016 through June 20, 2019 [6]. The diagnosis of COVID-19 was determined by a positive SARS-CoV-2 test within the 30 days prior to admission and up to 5 days after admission. In both cohorts, we excluded admissions with a primary diagnosis of DKA, using International Classification of Disease, 10th edition (ICD-10) codes of 'E10', 'E10.1', 'E10.10', 'E10.11'. The study was approved by the Intermountain Healthcare IRB # 1051342 under waiver of written consent.

In both cohorts, we analyzed cases for receipt of insulin and corticosteroids. We collected all blood glucose values, glycosylated hemoglobin (Hgb A1C), as well as general demographics, comorbidities, and clinical outcome data. We calculated the Elixhauser comorbidities score using previously described methods from ICD-10 coding data [7]. Our insulin sliding scale and eProtocol-insulin therapy define in target range glucose goal to be 90–140 mg/dL.

### 2.1. Statistical analysis

We tested group comparisons with Student *t*-test for continuous variables and  $\chi^2$  test for categorical variables. We utilized a stratified randomization for tertiary and secondary hospitals to obtain train and test datasets among both populations to tune the regression model with roughly a 20%/80% split. Regression was performed utilizing a linear regression. In the case of missing data, we performed analysis utilizing complete case analysis and imputation to normal values, both methods yielded similar results. We report the imputation dataset in our final model results. All analyses were carried out utilizing R version 3.6.1.

## 3. Results

We identified 13,268 patients with COVID-19 (36 patients were excluded for having a primary diagnosis of DKA), compared to 6673 patients with non-COVID-pneumonia. Of the patients with COVID-19, 286 patients were treated with eProtocol-Insulin, compared to 167 patients with non-COVID-pneumonia (Table 1). In the broader cohorts, we note patients with COVID-19 were younger (median age 59 vs 69,  $p < 0.001$ ) and had fewer comorbidities (Elixhauser 9 vs 19,  $p < 0.001$ ). They had lower mortality (8.2% vs 10.4%,  $p < 0.001$ ) and greater length of hospital stay (4 vs 3 days,  $P < 0.001$ ). We observed no difference in gender, or prevalence of diabetes among the cohorts though there was worse diabetic control (HgbA1C) among patients with COVID-19 (6.4 vs 6.1,  $p < 0.001$ ).

In the subset of patients receiving IV insulin, patients with COVID-19 were less likely to be female and have higher BMI. Both groups had similar prevalence of diabetes, but patients with COVID-19 had higher baseline HgbA1c values (8.4 vs 6.8%,  $p < 0.001$ ). There was no significant difference in mortality, although patients with COVID-19 had greater ICU lengths of stay (12 days vs 7.9 days). Patients with COVID-19 received more insulin (0.77 vs 0.54 units/Kg/day,  $p < 0.001$ ). In patients treated with IV insulin there was slightly less time in range (38% vs 41%  $p = 0.019$ ) for those with COVID-19. Similarly, in patients who received only SQ insulin, those with COVID-19 also had a lower percentage of glucose checks in range (25% vs 29%  $p < 0.001$ ).

Our regression models demonstrated that daily insulin dose, indexed for weight, was associated with COVID-19, age, diabetic status, HgbA1c, admission SOFA, ICU length of stay and receipt of corticosteroids (Table 2). These findings persisted among the subset of patients who received SQ insulin only and patients who received IV insulin. Our models demonstrated a significant interaction between COVID-19 and diabetes.

Time in range for our IV insulin protocol was correlated with ICU length of stay, diabetic control (HgbA1C) and prior history of diabetes (Table 3). Although patients with COVID-19 had significantly higher TIR than patients without, we observed no significant association between COVID-19 and TIR in our regression models after adjusting for diabetes, HgbA1c, and BMI.

Among patient who never received IV Insulin therapy and received SQ insulin we analyzed percent of glucose checks in range and this was negatively correlated with diabetic status, having Covid-19, HgbA1c, total steroids given and positively correlated with Elixhauser comorbidity score (Table 4).

Our sensitivity analyses found no difference in how missing data were handled.

## 4. Discussion

Patients with COVID-19 are more likely to have poorly controlled diabetes and higher BMI than comparable non-COVID pneumonia patients. When patient cohorts are adjusted for diabetic status, BMI, critical illness, and prior comorbidities, COVID-19 patients received higher daily amounts of insulin and had worse control across all subpopulations analyzed except those on IV insulin who had similar control and received higher amounts of insulin.

Prior observations noted challenges with maintaining euglycemia or TIR among COVID-19 patients. A single center retrospective observation of patients with COVID-19 noted lower TIR among patients with COVID-19 vs. patients without (44.4% vs. 68.5%) and higher daily insulin receipt [8]. Like our study, that study also demonstrated that patients with COVID-19 had higher HgbA1c values than those without COVID-19. Inferences from other studies are limited by the possibility that a COVID-19 diagnosis might reduce the frequency of glucose checks. In our study, the protocol was applied identically in COVID-19 and non-COVID-19 patients with a standard average time between glucose checks of 2 h in each group.

A mechanistic rationale for SARS-CoV-2 exerting an effect on insulin sensitivity has been suggested. Pancreatic  $\beta$ -cell function can deteriorate in some patients with COVID-19, resulting in new onset diabetes [9]. A key binding target for SARS-CoV-2 is angiotensin converting enzyme 2 (ACE 2), which is present within the respiratory lining and upregulated with diabetes and hyperglycemia [10]. Additionally, the inhibition of ACE 2 can result in downstream effects of upregulation of the renin-angiotensin-aldosterone system, increased oxidative stress, and decreased insulin sensitivity [11]. While these aspects of dysglycemia appear

**Table 1**  
Demographics expressed as n (%) or median (IQR) divided by patients who received intravenous insulin drip and those with only subcutaneous insulin receipt, and divided by Covid-19 pneumonia and non-covid 19 pneumonia.

	Intravenous drip		Subcutaneous Insulin Only	
	Covid-19 (N = 465)	Non Covid-19 (N = 167)	Covid-19 (N = 2890)	Non Covid-19 (N = 1238)
Female	160 (34.4%)	80 (47.9%)	1205 (41.7%)	574 (46.4%)
Age	60 (49–69)	64 (54–71)	65 (54–74)	70 (60–78)
Day 1 Sequential Organ Failure Assessment Score (SOFA)	6.0 (4.0–10)	8.0 (5.0–11)	4.0 (2.0–5.0)	4.0 (3.0–6.0)
Hospital length of stay	16 (9.0–24)	10 (5.0–16)	7.0 (4.0–12)	4.5 (3.0–7.0)
Intensive Care Unit length of stay	12 (6.0–22)	7.9 (3.8–12)	0.51 (0–7.6)	0 (0–3.4)
Presence of Diabetes	389 (83.7%)	122 (73.1%)	2136 (73.9%)	961 (77.6%)
Body Metabolic Index	32 (28–38)	29 (24–37)	32 (27–38)	30 (25–36)
Elixhauser score	17 (9–26)	23 (17–33)	14 (5–24)	23 (13–32)
30 Days Mortality	158 (34.0%)	51 (30.5%)	393 (13.6%)	133 (10.7%)
Units of Insulin/Kilogram/Day	0.77 (0.49–1.10)	0.54 (0.23–0.82)	0.12 (0.03–0.37)	0.08 (0.02–0.28)
Total Units of insulin	1100 (490–2000)	400 (140–760)	75 (17–250)	34 (10–120)
Total intravenous Units of Insulin	390 (130–840)	200 (70–410)	0 (0–0)	0 (0–0)
Total Steroid Equivalent dose	0.23 (0.16–60)	80 (0–250)	0.20 (0–20)	0 (0–55)
Hemoglobin A1C	8.4 (6.6–10)	6.8 (5.7–8.4)	6.9 (6.1–8.5)	6.8 (6.0–7.8)
Percent of Sliding Scale checks in range			25% (14%–41%)	29% (17%–50%)
Number of Glucose Checks			3.3 (2.3–4.1)	3.0 (2.0–3.8)
Hours on Protocol	95 (40–220)	72 (30–140)		
Hours in Range	37 (11–91)	28 (11–67)		
Intravenous Insulin Protocol % Time in Range	38% (25%–50%)	41% (29%–57%)		
Hours between protocol glucose checks	1.9 (1.7–2.1)	2.0 (1.9–2.2)		

**Table 2**  
Odds Ratio from Modeling for Units/Kg/Day for all inpatients.

Variable	OR (95% CI)	P value
Age	1 [1–1]	< 0.001
Female	1 (0.99–1.01)	0.976
Day 1 SOFA	1.01 (1–1.01)	< 0.001
Intensive Care Unit length of stay	1.01 (1.01–1.01)	< 0.001
Preexisting diagnosis of diabetes	1.12 (1.1–1.13)	< 0.001
Elixhauser Score	1 [1–1]	0.011
BMI	1 [1–1]	0.185
Covid infection	1.02 (1–1.05)	0.070
Hemoglobin A1c	1.08 (1.07–1.08)	< 0.001
Total steroid dose	1 [1–1]	< 0.001
Diagnosis of DM: covid infection	1.04 (1.02–1.05)	< 0.001
BMI:covid infection	1 [1–1]	0.039

**Table 3**  
Odds Ratio from modeling for Percentage Time in Range run only on ICU pts who had IV insulin drips.

Variable	OR (95% CI)	P value
Age	1 [1–1]	0.675
Day 1 SOFA score	1 (1–1.01)	0.176
Female	0.99 (0.97–1.03)	0.920
Intensive Care Unit length of stay	1 [1–1]	< 0.001
Preexisting diagnosis of diabetes	0.74 (0.87–0.95)	< 0.001
Elixhauser Score	0.99 [1–1]	0.01
BMI	1 [1–1]	0.613
Covid infection	0.89 (0.93–1.01)	0.127
Hemoglobin A1c	0.99 (0.98–0.99)	< 0.001
Total steroid dose	1 [1–1]	0.346

present among patients with COVID-19, it is likely that similar oxidative stress and dysregulation of the renin-angiotensin-aldosterone system also occur in other types of critical illness [12,13].

Strengths of our study include its multicenter environment, with a standardized insulin protocol applied in both groups. Our study has limitations common to all retrospective studies. Additional limitations include the comparison of a non-contemporaneous cohort, which might not account for secular

**Table 4**  
Odds Ratio from modeling for Percentage of Checks in Range run of SQ insulin.

Variable	OR (95% CI)	P value
Age	1 [1–1]	0.002
Day 1 SOFA score	1 [1–1]	0.495
Female	1.02 (1–1.03)	0.027
Intensive Care Unit length of stay	1 [1–1]	0.398
Preexisting diagnosis of diabetes	0.93 (0.91–0.95)	< 0.001
Elixhauser Score	1 [1–1]	0.039
BMI	1 [1–1]	0.100
Covid infection	0.97 (0.96–0.99)	< 0.001
Hemoglobin A1c	0.98 (0.98–0.98)	< 0.001
Total steroid dose	1 [1–1]	0.016

changes. However, the eProtocol-Insulin did not change throughout the study period, and the protocol has extremely high clinician compliance.

In summary, hospitalized patients with COVID-19 pneumonia who receive insulin for glycemic control require more IV and SQ insulin than the non-COVID-19 pneumonia counterparts.

**Sources of support**

None to declare.

**Data availability**

In order to protect patient privacy and comply with relevant regulations, identified data are unavailable. Requests for deidentified data from qualified researchers with appropriate ethics board approvals and relevant data use agreements will be processed by the Intermountain Office of Research, [officeofresearch@imail.org](mailto:officeofresearch@imail.org).

**Declaration of competing interest**

We have no conflicts of interest to disclose. All authors have a) contributed substantively to the conception, design, or analysis and interpretation of the data, b) contributed substantively to the drafting of the manuscript or critical revision for important

intellectual content, c) given final approval of the version to be published, and d) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Intermountain Healthcare IRB #1051342.

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D.K. conceptualized and designed the study, performed data gathering and the analysis, interpreted results, drafted manuscript, approved final manuscript for submission and attests to the veracity of the data. J.O., E.H., I.P. contributed to the discussion and reviewed/edited the manuscript. M.L. assisted with conceptualization and design of the study, assisted with drafting and editing of the manuscript.

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