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Moderately hyperglycemia as an independent prognostic factor for the worse outcome of COVID-19

Saeed Nateghi a, Mohammad Mahmoudi Gomari b, Yousef Jalali roudsari a, Alireza Foroughi a, Fariba Mansouri c, Ashkan Shiva a, Ali Nasrrollahizadeh d, Zohreh Nasiri a, Neda Faraji a,⁎

a Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran
b Department of Medical Biotechnology, Faculty of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran
c Respiratory Department, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
d School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT
Background: Blood sugar (BS) has been proposed as a prognostic factor for COVID-19. In this historical cohort study we evaluated the association between admission time BS and COVID-19 outcome.

Methods: First, hospitalized COVID-19 patients were divided into three groups; Non-diabetic patients with BS < 140 mg/dl (N = 394), non-diabetic patients with BS ≥ 140 mg/dl (N = 113) and diabetic patients (N = 315). Mortality, ICU admission, and length of hospital stay were compared between groups and odds ratio was adjusted using logistic regression.

Results: After adjustment with pre-existing conditions and drugs, it was shown that non-diabetic patients with BS ≥ 140 mg/dl are at increased risk of mortality (aOR 1.89 (0.99–3.57)) and ICU admission (aOR 2.62 (1.49–4.59)) even more than diabetic patients (aOR 1.72 (1.07–2.78) for mortality and aOR 2.28 (1.47–3.54) for ICU admission).

Conclusions: Admission time hyperglycemia predicts worse outcome of COVID-19 and BS ≥ 140 mg/dl is associated with a markedly increase in ICU admission and mortality.

1. Introduction

Since the beginning of the COVID-19 pandemic, a growing concern raised surrounding the management of health care systems [1]. Shortage of facilities during surge of the pandemic necessitates patients screening to identify patients with severe disease. This contributes to cautiously allocate ventilators and other facilities according to priorities [2]. Prognostic factors are widely used for different diseases to predict the outcome of diseases and modulate it by early intervention [3]. Previous studies attempted to introduce several prognostic factors to identify COVID-19 patients, at high risk of severe outcome. Herein, it was observed that increased C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer and decreased platelet count and lymphocyte count are associated with poor outcome of COVID-19 [4]. Similarly, increased ferritin and prolactin prognosticate severe COVID-19 [5].

Diabetes is a risk factor for poor outcome of several diseases such as cardiovascular diseases, cancers and infectious diseases [6]. In addition, diabetes increases the risk of infectious diseases, particularly among older people [7]. There is a bidirectional relationship between hyperglycemia and infection. Hyperglycemia can weaken effective immune response to pathogens [8]. In exchange, extensive release of inflammatory cytokines and stress hormones during infection and other inflammatory diseases induces insulin resistance and hyperglycemia [9]. However, stress hyperglycemia has been proposed as an essential protective mechanism [9]. Better glycemic control decreases the risk of infection [7]. Diabetes and hyperglycemia are common findings among COVID-19 patients and they are associated with worse outcomes of COVID-19 [10]. In this historical cohort study, we compared COVID-19 outcomes between diabetic patients, non-diabetic patients with hyperglycemia and non-diabetic patients without hyperglycemia. Next, we assessed which range of admission time BS is associated with worst outcome of COVID-19. It is the first study that reports the most dangerous zone of admission time BS for COVID-19.

⁎ Corresponding author.
E-mail address: nedafaraji1368@gmail.com (N. Faraji).

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2. Methods and materials

2.1. Study population and source of data

This retrospective study was performed in Baharloo Hospital, Tehran. Hospitalized COVID-19 patients, entered this historical cohort study. According to the type of study, which was a cross-sectional ran. Hospitalized COVID-19 patients, entered this historical cohort -2. Methods and materials

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CT-scan, in favor of COVID-19. Patients with at least one of the following because of their severe signs and symptoms and a documented PCR or performed for patients without sufficient response to nasal O

3. Treatment protocol

Respiratory support and hydration were provided. Intubation was performed for patients without sufficient response to nasal O2 or NIV (non-invasive ventilation). Symptomatic management was considered for fever, pain, vomiting and diarrhea. Use of anti-inflammatory and anti-viral drugs with significantly different distribution among groups, has been adjusted for assessment of odds ratio.

4. Groups of patients and outcomes

First of all, we divided patients into three groups, diabetic patients, non-diabetic patients with admission time BS < 140 mg/dl and non-diabetic patients with admission time BS ≥ 140 mg/dl [11,12]. Our definition for diabetes was based on patients’ histories. Death, ICU admission, length of hospital stay were compared between groups as the outcomes of this study. In addition, crude odds ratio and adjusted odds ratio were assessed for these outcomes.

5. Data analysis

Quantitative traits are shown as mean (SD) and qualitative traits are presented as frequencies and percentages. Differences in means were evaluated by student’s t-test. Differences in percentages were measured by chi-square test. Data were analyzed by Stata software version 14 and p value < 0.05 was considered significant. Logistic regression was used for adjustment of odds ratio. In order to recognize the confounders, we assessed the demographic features of each group such as age, sex and body mass index (BMI). Further, we compared their pre-existing conditions such as cardiovascular diseases (defined as ischemic heart diseases, congestive heart failure and valvular heart diseases), hypertension, diabetes, stroke, smoking, malignancy, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, chronic kidney disease (CKD), systemic lupus erythematosus, rheumatoid arthritis, dyslipidemia and thyroid diseases (hypo- and hyperthyroidism). Demographic features, comorbidities and drugs with significantly different distribution among groups, were used for adjustment of odds ratio.

6. Results

According to our inclusion criteria, 822 patients entered this study. Among them, 394 non-diabetic patients with admission time BS < 140 mg/dl entered group 1, 113 non-diabetic patients with admission BS ≥ 140 mg/dl entered group 2 and 315 patients with history of diabetes entered group 3. Their age was 57.52 ± 16.79 years and diabetic pa-

Table 1 Patients’ co-existing conditions and types of medication used for them.

|                      | All patients (n = 822) | Group 1 (n = 394) | Group 2 (n = 113) | Group 3 (n = 315) | P value |
|----------------------|-----------------------|-------------------|-------------------|-------------------|---------|
| Age                  | 57.52 ± 16.79         | 53.85 ± 16.52     | 56.42 ± 16.72     | 63.49 ± 16.90     | < 0.0001|
| BMI                  | 27.58 ± 5.70         | 27.35 ± 5.78      | 26.75 ± 5.80      | 28.08 ± 6.09      | 0.017   |
| Male                 | 461 ± 227            | 76 ± 227          | 69 ± 227          | 165 ± 227         | 0.195   |
| Age > 60 years       | 394 (47.6)           | 144 (36.3)        | 38 (33.6)         | 189 (60.0)        | < 0.0001|
| Hypertension         | 281 ± 227            | 78 ± 227          | 20 ± 227          | 183 (58.1)        | < 0.0001|
| Stroke               | 58 (7.1)             | 24 (6.1)          | 9 (8.8)           | 25 (7.9)          | 0.585   |
| Current or former smoker (n = 609) | 62 (7.5)          | 23 (5.8)          | 11 (9.7)          | 28 (8.9)          | 0.198   |
| Dyslipidemia         | 51 (6.2)             | 15 (3.8)          | 1 (0.9)           | 35 (11.1)         | < 0.0001|
| Cardiovascular diseases † | 131 (16.2)       | 46 (11.7)         | 16 (14.2)         | 69 (21.9)         | 0.001   |
| Thyroid diseases †   | 32 (3.9)             | 13 (3.3)          | 3 (2.7)           | 16 (5.1)          | 0.364   |
| Respiratory diseases | 38 (4.6)             | 17 (4.3)          | 10 (8.8)          | 11 (3.5)          | 0.062   |
| Rheumatologic diseases ‡ | 9 (1.1)            | 4 (1)             | 1 (0.9)           | 4 (1.3)           | 0.924   |
| CKD                  | 24 (2.9)             | 10 (2.5)          | 0                 | 14 (4.4)          | 0.045   |
| Bilastinum           | 357 (43.4)           | 182 (46.2)        | 41 (36.3)         | 134 (42.5)        | 0.159   |
| Ribavirin            | 134 (16.3)           | 60 (15.2)         | 21 (18.6)         | 53 (16.8)         | 0.661   |
| Corticosteroids      | 141 (17.2)           | 54 (13.7)         | 19 (16.8)         | 68 (21.6)         | 0.022   |
| ACE inhibitors/ARB   | 90 (10.9)            | 25 (6.3)          | 10 (8.8)          | 55 (17.5)         | < 0.0001|
| PPI                  | 381 (46.4)           | 179 (45.4)        | 50 (44.2)         | 152 (48.3)        | 0.672   |

Footnote: Group 1: Non-diabetic patients with BS < 140 mg/dl. Group 2: Non-diabetic patients with BS > 140 mg/dl. Group 3: Diabetic patients. Data are presented as number (percentage). Age and BMI are shown as mean (SD). † Cardiovascular diseases were defined as ischemic heart diseases, congestive heart disease, valvular heart diseases, stroke and peripheral vascular disease. ‡ Thyroid diseases were defined as hypothyroidism and hyperthyroidism. † Respiratory diseases were considered as COPD, tuberculosis and asthma. ‡ Rheumatologic diseases were defined as systemic lupus erythematos and rheumatoid arthritis. PPI Smoking data were available for 609 patients. Angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), body mass index (BMI), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), proton pump inhibitor (PPI).
outcomes, they were used for adjustment of odds ratio (Table 1). Of all patients, 15.1% died after hospitalization and 19.8% were admitted to ICU. Mortality was significantly higher in group 3 than group 2. Group 1 had significantly lower mortality rate (Fig. 1). ICU admission followed the same pattern. Diabetic patients had significantly longer length of hospital stay (Table 2).

According to crude odds ratio, diabetes was associated with increased mortality (95% CI, OR 2.19 (1.43–3.35), \( p < 0.0001 \)), ICU admission (95% CI, OR 3.02 (2.04–4.48), \( P < 0.0001 \)) and length of hospital stay (95% CI, OR 1.57 (1.15–2.16), \( p = 0.005 \)). Further, non-diabetic patients with BS ≥ 140 mg/dl had increased risk of ICU admission (95% CI, OR 2.37 (1.39–4.03), \( p = 0.001 \)) and partly mortality (95% CI, OR 1.74 (0.96–3.13), \( p = 0.066 \)). After adjustment of odds ratio with age and sex, it was shown that non-diabetic patients with BS ≥ 140 mg/dl had worst outcomes, according to mortality (95% CI, aOR 1.92 (1.04–3.58), \( p = 0.038 \)) and ICU admission (95% CI, aOR 2.57 (1.48–4.46), \( p = 0.001 \)). Increased mortality (95% CI, aOR 1.62 (1.04–2.53), \( p = 0.032 \)) and ICU admission (95% CI, aOR 2.45 (1.63–3.69), \( p < 0.0001 \)) were also observed among diabetic patients but lower than group 2. However, even after adjustment of age and sex just diabetes was associated with increased length of hospital stay (95% CI, aOR 1.55 (1.11–2.15), \( p = 0.009 \)). After multiple adjustment of odds ratio with age, sex, hypertension, cardiovascular, respiratory diseases, CKD, corticosteroids, ARBs and ACE inhibitors, it was shown that BS ≥ 140 mg/dl among non-diabetic patients considerably increased mortality (95% CI, aOR 1.89 (0.99–3.57), \( p = 0.050 \)) and ICU admission (95% CI, aOR 2.62 (1.49–4.59), \( p = 0.001 \)) but could not significantly affect length of hospital stay. Diabetes was associated with increased mortality (95% CI, aOR 1.72 (1.07–2.78), \( P = 0.026 \)) and ICU admission (95% CI, aOR 2.28 (1.47–3.54), \( p < 0.0001 \)) but its impact on mortality and ICU admission was lower than BS ≥ 140 among non-diabetic patients. In addition, after multiple adjustment, it was revealed that diabetes could not significantly increase length of hospital stay (Table 3).

7. Discussion

Since the outbreak of COVID-19 in Wuhan, China several prognostic factors have been proposed to predict the outcome of COVID-19 [5,13]. Diabetes is a prevalent comorbidity of COVID-19 and previous studies, consistent with this study, indicated that diabetes predicts poor outcome of COVID-19 [14,15]. Previously, it was uncovered that hyperglycemia and diabetes are independent predictors for death in severe acute respiratory syndrome (SARS) patients [16]. It was shown that higher level of admission time BS predicts poor outcome of COVID-19. Similarly, increase of BS after during hospital stay was associated with severe outcome of COVID-19 [17]. It was reported that hyperglycemia is associated with worse outcome of COVID-19, compared with diabetes. Further, it was reported that hyperglycemia prolongs length of hospital stay and markedly increases mortality [18]. Wang et al. reported that fasting blood sugar (FBS) ≥ 7 mmol (126 mg/dl) at admission predicts lower survival of patients [19]. Li et al. found that newly diagnosed diabetes is associated with the worst outcomes followed by known diabetes and hyperglycemia, respectively [20].

Severe acute respiratory coronavirus 2 (SARS-CoV-2) stimulates immune system and promotes the release of numerous pro-inflammatory cytokines [21]. The pro-inflammatory metabolic state can induce severe insulin resistance which results in hyperglycemia [22]. Previous studies uncovered the molecular mechanisms which mediates insulin resistance in hepatocytes during cytokine storm [23]. Moreover, chronic inflammation has been implicated in insulin resistance [24]. Hyperglycemia is associated with higher concentrations of interleukin 6 (IL6) and D-dimer in patients with COVID-19 [25,26]. This can show that hyperglycemia is a sign of underlying cytokine storm which is associated with poor prognosis of COVID-19. Hyperglycemia and diabetes increase urinary excretion of ACE2 [27]. Likewise, ACE2 expression increases in animal model of diabetes [28,29]. SARS-CoV-2 uses ACE2 for its entry into the host cells and upregulation of ACE2 can lead to higher viral load [30,31]. Further, ACE2 is vigorously expressed in the pancreas and SARS-CoV-2 can invade pancreatic islets [32]. This may result in insufficient insulin secretion and hyperglycemia.

In our study, non-diabetic patients with BS ≥ 140 mg/dl had the worst outcomes regarding mortality and ICU admission. Likewise, diabetes was associated with worse outcomes and increase in mortality and ICU admission. Moreover, it was shown that BS ≥ 140 mg/dl independently was associated with increase in mortality and ICU admission, regardless of the presence or absence of diabetes. However, parts of our results were not statistically significant because of inadequate power of this study.

8. Conclusion

Taken together, this study indicated that admission time BS ≥ 140 mg/dl predicts higher mortality and ICU admission among hospitalized COVID-19 patients. Moreover, mortality and ICU admission were more common among non-diabetic patients with admission time BS ≥ 140 mg/dl, even more than diabetic patients.

Limitations

Our investigation is a cross-sectional study and encountered several hurdles such as low sample size, lack of general medication detail of patients, lack of patient BMI information, and we relied on the histories of patients for parts of the data.

![Kaplan-Meier survival estimates](image_url)
Table 3

| Outcome: Death | Model 1 odds ratio | P-value | Model 2 odds ratio | P-value | Model 3 odds ratio | P-value |
|----------------|--------------------|---------|--------------------|---------|--------------------|---------|
| **Group 1** | 1 | | 1 | | | |
| **Group 2** | 1.74 (0.96–3.13) | 0.066 | 1.92 (1.04–3.58) | 0.038 | 1.89 (0.99–3.57) | 0.050 |
| **Group 3** | 2.19 (1.43–3.35) | <0.0001 | 1.62 (1.04–2.53) | 0.032 | 1.72 (1.07–2.78) | 0.026 |

**Outcome: ICU Admission**

| **Group 1** | 1 | | 1 | | | |
| **Group 2** | 2.37 (1.39–4.03) | 0.001 | 2.57 (1.48–4.46) | 0.001 | 2.62 (1.49–4.59) | 0.001 |
| **Group 3** | 3.02 (2.04–4.48) | <0.0001 | 2.45 (1.63–3.69) | <0.0001 | 2.28 (1.47–3.54) | <0.0001 |

**Declaration of Competing Interest**

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