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The prognostic role of hyperglycemia and glucose variability in covid-related acute respiratory distress Syndrome

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ABSTRACT

Aims: Due to heterogeneity on the prognostic role of glucose values and glucose variability in Novel Coronavirus (COVID) disease, we aimed at assessing the prognostic role for Intensive Care Unit (ICU) death of admission hyperglycaemia, peak glycemia and glucose variability in critically ill COVID patients:

Methods: 83 patients consecutively admitted for COVID-related Acute Respiratory Distress Syndrome (ARDS) from from 1st March to 1st October 2020.

Results: Non survivors were older, with more comorbidities and a more severe disease. Corticosteroids were used in the majority of patients (54/83, 65%) with no difference between survivors and non survivors. Mean blood glucose values, (during the first 24 and 48 h, respectively), were comparable between the two subgroups, as well as SD 24 and CV 24. During the first 48 h, survivors showed significantly lower values of SD 48 ($p < 0.001$) and CV 48, respectively ($p < 0.001$) than non survivors.

Conclusions: in consecutive COVID-related ARDS patients admitted to ICU hyperglycemia (>180 mg/dl) is more common in non survivors who also showed a significantly higher glucose variability in the first 48 h since ICU admission. Our findings point to the clinical significance of in-ICU glucose control in severe COVID patients.

1. Introduction

Hyperglycaemia (stress-related hyperglycemia) is quite common in critically ill patients, and, though in the lack of an universal threshold for stress-related hyperglycamia, it was associated with increased morbidity and mortality in critical illness [1–3]. Also glycemic variability was recognized as a strong independent predictor of mortality among critically-ill patients [4,5].

To date, evidence on the prognostic role of hyperglycemia in COVID disease is scarce and heterogenous mainly due to differences in clinical characteristics of study populations (ie. with or without previously known diabetes, and different degrees of disease severity).

The present investigation was aimed at assessing the prognostic role for ICU death of admission hyperglycaemia, peak glycemia and glucose variability (as indicated of the standard deviation of mean glucose levels and the coefficient

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of variation of glucose) in 83 patients consecutively admitted for COVID-related Acute Respiratory Distress Syndrome (ARDS) in our ICU (which is an ECMO referral center) from 1st March to 1st October 2020.

2. Methods

2.1. Study population

In this case series study we enrolled all patients with COVID-19 ARDS consecutively admitted to our ICU (which is an ECMO referral center) from 1st March to 1st October 2020. The study protocol was approved by our Ethical Committee (n.17024, approved on March 31th 2020). ARDS was defined according to the Berlin definition [6].

2.2. Data collection

For each patient the following clinical variables were recorded in a dedicated database: age, gender, body mass index (BMI) and risk factors (previously known diabetes, hypertension, history of heart disease). Charlson comorbidity index was calculated based on medical history [7]. The simplified acute physiology score (SAPS) II was also calculated [8].

On ICU admission we measured: C-reactive Protein (CRP, mg/dl) creatinine (mg/dl), Lactose dehydrogenase (LDH, UI/L), alanine transaminase (ALT, UI/L), D-dimer (ng/ml)and interleukin 6 (IL-6, pg/ml).

2.3. Glucose management

A predefined insulin protocol was used in all patients for management of hyperglycemia and intensive insulin therapy was administered in patients with significant hyperglycemia (that is plasma glucose > 150 g/l) [1–3,9].

According to our protocol [2,9], glucose values were measured four times a day, and the peak glucose was determined among all values measured during ICU stay [10–12]. Glucose values for the first 24 and 48 h were recorded to calculate the following parameters:

(a) Mean blood glucose level as arithmetic mean of all recorded glucose values for each patient for the first 24 h (Mean BG 24) and for the first 48 h (Mean BG 48);
(b) Standard deviation (SD) of mean glucose levels for the first 24 h (SD 24) and for the first 48 h (SD 48);
(c) Coefficient of variation (CV) of glucose (derived as a percentage of SD to mean blood glucose) for the first 24 h (CV 24) and for the first 48 h (CV48 and SD48 (CV 48) [2,4,5,13].

Data were prospectively recorded and retrospectively analyzed.

2.4. Outcome

The primary endpoint for the analysis was in-ICU mortality (defined as death before hospital discharge).

2.5. Statistical analysis

Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean ± SD or median (interquartile range]. Between-groups (survivors and nonsurvivors] comparisons were assessed by means of Fisher's exact test and Student's t-tests (or Mann–Whitney *U* test when needed], respectively . Statistical analysis was performed with the use of PASW 17.0 statistical package (SPSS Inc, Chicago, IL]. A two-tailed p value < 0.05 was considered statistically significant.

3. Results

Our population comprises 83 consecutive patients with COVID-related ARDS admitted to our ICU (Table 1). The study population included mainly males (83%), and hypertension was the commonest risk factor, being detectable in 78% of cases. Previously known diabetes was observed in 33 patients (40%). Most patients (62%) were mechanically ventilated. In our series ICU mortality was 36% (30/83).

In the comparison between survivors and non survivors (Table 1), non survivors were older ($p < 0.001$), with more comorbidities, as indicated by a higher Charlson's index ($p < 0.001$) and with a more severe disease, inferred by a higher SAPS II index ($p < 0.001$). Higher values of creatinine were observed in no survivors ($p = 0.032$).

Corticosteroids were used in the majority of patients (54/83, 65%) with no difference between survivors and non survivors (survivors: 33; non survivors: 21, $p = 0.477$, chi square test).

Table 2 shows glucose values and glucose variability parameters (both at 24 and 48 h since ICU admission) in the overall population and in the comparison between survivors and non suvivor patients. No difference was observed in the two subgroups in admission glucose values but the frequency of admission glycemia > 180 mg/dl was significantly higher in non survivors ($p = 0.036$). Peak and nadir glycemia during ICU stay were comparable between the two subgroups, but the frequency of hypoglycemia (<70 mg/dl) was higher in non survivors ($p = 0.042$). Mean blood glucose values, both during the first 24 and 48 h, respectively, were comparable between survivors and non survivors, as well as SD 24 and CV 24. During the first 48 h since ICU admission, survivors showed significantly lower values of SD 48 ($p < 0.001$) and CV 48, respectively ($p < 0.001$).

4. Discussion

The main findings of the present investigation, performed in consecutive COVID-related ARDS patients admitted to ICU, are as follows: a) hyperglycemia (>180 mg/dl) is more common in non survivors; b) glucose variability in the first 48 h since ICU admission is significantly higher in non survivors. Overall, our findings point to the clinical significance of glucose control in severe COVID patients during ICU stay.

To date, evidence on the prognostic role of hyperglycemia in COVID disease is scarce and heterogenous mainly due to differences in clinical characteristics of study populations

Table 1 – Clinical Characteristics.

		Survivors	Non survivors	
Number	83	53	30	
Age (mean ± SD)	67 ± 14	65 ± 15	76 ± 11	< 0.001(t)
Gender (Males, n, %)	70 (83%)	31	29	
BMI (Kg/m2) (mean ± SD)	29 ± 4	29 ± 5	28 ± 4	0.351 (t)
Risk cardiovascular factors (n,%)				
Known diabetes	33 (40%)	17	16	0.057*
Hypertension	65 (78%)	40	25	0.403*
Heart disease	34 (41%)	20	14	0.426*
Charlson's index	3.8 ± 2	3 ± 2	5 ± 2	<0.001(t)
MV (n. %)	52 (62%)	31	21	0.297*
NIV (n.%)	35 (42%)	25	12	0.527*
P/F	100 ± 68	90 ± 42	81 ± 44	0.359(t)
SAPS II (mean ± SD)	29 ± 7	26 ± 7	33 ± 6	<0.001 (t)
LOS (days)(median IQR)	10.5 (7.5–19)	11 (8–22.5)	9 (7–16)	0.291 KW
Laboratory data				
Creatinine (mg/dl median IQR)	1 (0.71–1.69)	0.8 (0.6–1.3)	1 (0.88–2.4)	0.032 KW
LDH (IU/L median IQR)	367 (319–460)	359 (307–430)	369 (298–461)	0.756 KW
D-dimer (ng/ml median IQR)	1801 (1166–3300)	1724 (1051–2981)	2003 (1236–3258)	0.384 KW
CRP (mg/dl median IQR)	95 (29–190)	86 (21–161)	117 (33–218)	0.524 KW
IL-6 (pg/ml, median IQR)	79 (19–201)	79 (19–201)	60 (15–211)	0.846 KW

BMI: body mass index, MV: mechanical ventilation, NIV: non invasive ventilation, P/F: PO2/FiO2 ration, SAPS II: simplified acute physiologyscore; LOS: lenght of stay, LDH: lactic dehydrogenase; CRP: C Reactive protein, IL-6: interleukin 6, IQR: interquartile rante, KW: Kruskal-Wallis test; (t): Student *t* test, *: chi square test.

Table 2 – Glucose values and glycamic variability indexes in the comparison between survivors and no survivors.

		Survivors	Non survivors	
Number	83	53	30	
Admission glycemia (mg/dl) median IQR	133 (120–169)	131 (118–152)	145 (123–180)	0.154#
Admission glycemia > 180 mg/dl (n.%)	13 (16%)	5 (9%)	8 (27%)*	0.036 *
Peak glycemia (mg/dl) median, IQR	219 (180–250.5)	220(186–245)	223 (189–255)	0.660#
Nadir glycemia	93 (78–106)	91 (78–106)	92(75–105)	0.867#
Hypoglycemia (<70 mg/dl) (n.%)	11 (12%)	2 (3%)	5 (16%)*	0.042*
Mean 24 (mg/dl) median IQR	142 (123.7–163.5)	135 (120–163)	145 (129–167)	0.201 #
SD 24	24 ± 18	22 ± 15	27 ± 18	0.113 (t)
CV 24	16 ± 10	15 ± 9	17 ± 10	0.353 (t)
Mean 48 (mg/dl) median IQR	143.5 (124–167)	141 (120–160)	149 (128–170)	0.115#
SD 48	27 ± 16	25 ± 15	39 ± 16	<0.001 (t)
CV48	18 ± 8	17 ± 8	25 ± 9	<0.001 (t)

SD: standard deviation; CV: coefficient of variation, IQR: interquartile range. #Kruskal-Wallis test. *chi square test. (t): Student *t* test.

(ie. patients with or without previously known diabetes, and different degrees of disease severity).

In non critically ill patients, elevated glucose values were associated with a worse prognosis [14–22], but heterogeneity in study design can be detected in these investigations concerning study population (diabetics versus non diabetics) and blood glucose measurements (admission, fasting, in hospital glucose values). In a two-center retrospective investigation [17] (605 COVID patents without previous diagnosis of diabetes) fasting blood glucose (FBG $\geq$ 7.0 mmol/l) at admission was an independent predictor for 28-day mortality . However, no data were provided on the percentage of patients with severe COVID disease (admitted to ICU) nor on the standard protocol of in-hospital glucose management. The association between hyperglycemia and increased risk of death was confirmed in further studies performed in non severe COVID disease [18,19] and in non diabetics [21], but evidence is overall not univocal. Fasting blood glucose was related to the occurrence of ARDS, but not with death in 191 COVID [20] non critical patients.

The present investigation includes the largest population of critically ill COVID patients, in whom glucose values (admission, peak and nadir) were investigated throughout ICU stay. In intensive care patients with COVID disease, several factors may exacerbate hyperglycaemia and insulin resistance, in primis bed rest, medications (i.e. vasopressors and corticosteroids) and systemic inflammatory activation [23]. We also assessed glucose variability which itsefl is affected by hyperglycemia, insulin resistance, disease severity and also by management, thus being considered a modifiable factor.

Regarding hyperglycemia, in our population admission glycemia did not differ between survivors and non survivors, but the percentage of admission glycemia > 180 mg/dl was

higher in non survivors than in survivors, This was probably due to both severity of disease and the high use of corticosteroids in our series. Corticosteroids are known to glucose tolerance (by the incresed in gluconeogenesis in the liver), and to reduce glucose uptake and utilisation in peripheral tissues [24]. However, in COVID-related ARDS, corticosteroid use are highly recommended [25], since they were reported to be associated with reduced mortality and lower need of mechanical ventilation.

To date, glycemic variability was specifically investigated in COVID disease only by Zhu et al [15] who, in a retrospective analysis, documented that in patients with pre-existing type 2 diabetes, glycaemic variability during hospitalization within 3.9 –10.0 mmol/l (that is well-controlled glucose) was associated with markedly lower mortality compared with patients with poorly controlled blood glucose (glycaemic variability more than mmol/l) [15]. However, patients aged > 75 years, and those with acute lethal organ injury or acute decompensated or end stage organ dysfunction were excluded. Recently, Shen et al [26] observed, by means of continuous glucose monitoring, that patients of diabetes and COVID disease (35 patients) had an increase risk of outcomes with glucose values > 160 mg/dl and < 70 mg/dl and a high coefficient of variation.

In this context, this is the first investigation assessing glucose variability in consecutive COVID patients with severe disease, admitted to ICU. We observed that 48 h glucose variability (as indicated by SD48 and CV48) was higher in non survivors compared to survivors. This finding may underscore the prognostic role of glucose management in these critically ill patients.

The clinical impact of glycemic control during hospitalization may be due to several reasons. Hyperglycemia per se is known to induce activation a pro-thrombotic status mainly through oxidative stress and non-enzymatic glycation [27,28]. In diabetic patients with COVID disease an increase of D-dimer was observed compared to people without diabetes [29]. Moreover, an acute increase of glycemia is associated with a huge increase of inflammatory mediators [30] and, more specific for COVID disease, to the binding of SARS-CoV-2 to ACE2 [31], thus favouring the cellular intrusion of the virus and potentially leading to a higher disease severity. However, this process is known to be, at the beginning, reversible (the so called reversible glycosilation") [32]. Thus, it can be supposed that strict glycemic control and avoidance of acute hyperglycemia also during ICU stay might result in a reduced inflammatory response and a lower ACE2 binding capacity for the virus [24,33]. Hower, to date there is no agreement whether an aggressive correction of hyperglycemia (with an increased risk of hypoglycemia) may be beneficial in critically ill patients, even if avoidance of blood glucose variations is considered advisable in these patients [34–36].

On a clinical point of view, glucose management in patients with severe COVID disease, deserves careful attention by intensivists since glucose values are influenced in these patients by both the systemic inflammatory response (due to critical illness and COVID disease) and therapies (in primis corticosteroid therapy).

Further clinical research should be aimed at identifying the optimal range of in-hospital glucose values and at assessing their impact on prognosis, in-hospital complications and disease progression.

4.1. *Limitation of the study*

We acknowledge that continuous glucose monitoring would have captured more accurately nadirs and peaks. However, in every day clinical practice in intensive care, glucose assessment is performed by means of blood gas analysis and the results of the present investigation strongly suggest the clinical role of glucose variability and glucose management in treating critical care patients with COVID disease. Though this is a monocentric investigation, we believe that our "take home message" (a clinical focus on in ICU glucose management in critically ill patients with COVID disease) may be extended to other centers. Due to the lack of glycosylated hemoglobin, it cannot be excluded that the patients with stress hyperglycemia may comprise some patients with previously unknown diabetes. Further studies should be performed specifically addressing this issue.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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