Glycemic Variability Is Associated With All-Cause Mortality In COVID-19 Patients With ARDS

Findings From The COVAS Cohort

Bojan Hartmann

University Hospital Aachen

Marlo Verket

University Hospital Aachen

Paul Balfanz

University Hospital Aachen

Niels-Ulrik Hartmann

University Hospital Aachen

Malte Jacobsen

University Hospital Aachen

Julia Brandts

University Hospital Aachen

Michael Dreher

University Hospital Aachen

Nils Kossack

WIG2 – Scientific Institute for Health Economics and Health System Research

Dennis Häckl

WIG2 – Scientific Institute for Health Economics and Health System Research

Nikolaus Marx

University Hospital Aachen

Dirk Müller-Wieland (✉ dirmueller@ukaachen.de)

University Hospital Aachen

Research Article

Keywords: Glycemic variability, COVID-19, ARDS, Cardiovascular disease, Type 2 diabetes

Posted Date: January 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1111538/v1>

Abstract

There is high mortality among intensive care unit (ICU) patients with acute respiratory distress syndrome (ARDS) caused by coronavirus disease 19 (COVID-19). Important factors for COVID-19 mortality are diabetes status and elevated fasting plasma glucose (FPG). However, the effect of glycemic variability on survival has not been explored in patients with COVID-19 and ARDS. This single-centre cohort-study compared several metrics of daily glycemic variability (DGV) for goodness-of-fit in patients requiring mechanical ventilation due to COVID-19 ARDS in the ICU at University Hospital Aachen, Germany. 106 patients had moderate to severe ARDS (P/F ratio median [IQR]: 112 [87-148] mmHg). Continuous HRs showed a proportional increase in mortality risk with DGV. Multivariable unadjusted and adjusted Cox-models showed a statistically significant difference in mortality for DGV (HR: 1.02, (P)<0.001, LR(P)<0.001; HR: 1.016, (P)=0.001, LR(P)<0.001, respectively). Kaplan-Meier estimators yielded a shorter median survival (25 vs. 87 days) and higher likelihood of death (75% vs. 31%) in patients with DGV $\geq$ 25.5mg/dl (P<0.0001). High glycemic variability during ICU admission is associated with significant increase in all-cause mortality for patients admitted with COVID-19 ARDS to the ICU. This effect persisted even after adjustment for clinically predetermined confounders, including diabetes, procalcitonin and FPG levels at baseline.

Introduction

Acute respiratory distressed syndrome (ARDS) caused by the coronavirus disease 19 (COVID-19) has been associated with a high mortality rate for patients in the intensive care unit (ICU). Recently, pooled global mortality rate of patients who have been admitted with COVID-19 associated ARDS to ICU is estimated to be 39% (95% CI:23-56%)¹. This high mortality in COVID-19 with ARDS highlights the importance on identifying clinical features and various biomarkers as predictors of poor disease outcome over time. Furthermore, type 2 diabetes (T2D), obesity, hypertension, and cardiovascular diseases increase severity and fatal outcome in patients with COVID-19 associated ARDS²⁻³.

Fasting plasma glucose (FPG) level but not HbA1c at admission has been shown to be a predictor for mortality outcome in patients with COVID-19 and ARDS. Previous studies suggest that elevated glucose levels on admission^{4,5} and plasma glucose fluctuations in the early phase⁶ of hospitalisation in COVID-19 patients predict adverse outcome regardless of diabetes status. Recently, a multi-centre study⁷ in Italy demonstrated that by patients who were admitted with COVID-19 to ICU, glucose levels were significantly higher in non-survivors than in survivors. However, when considering the effect of FPG, these studies have concentrated on the absolute values of FPG and not the variability of glucose over time.

To our knowledge, there have been no previous studies that investigated glucose variability over the course of ICU admission. In this report, we evaluate the effect of glucose level parameters and glucose variability on patient survival, specifically in patients admitted to the ICU with ARDS due to COVID-19.

Results

A total of 106 patients with ARDS caused by COVID-19 were included in this retrospective analysis and 53 (50%) of patients were defined as survivors. Characteristics in this cohort are summarized in Table 1. The majority were diagnosed with moderate to severe ARDS on admission (P/F ratio median [IQR]: 112 [87-148] mmHg). In total, 32 (30%) had a previous T2D diagnosis and 10 patients with HbA1c $\geq$ 6.5% (48 mmol/mol) had newly diagnosed T2D. We identified 58 (54%) patients with hyperglycemia (FPG >140 mg/dl) on admission to the ICU, of which 33 (56%) had no prior diagnosis of T2D.

Utilizing a Cox-PH model (adjusted for age, sex and history of T2D) for FPG on admission as a continuous covariate, we replicated previous findings that high FPG on admission is a predictor of mortality. This model showed statistical significance for FPG and the model (HR: 1.00 [95% CI, 1.00-1.01], Fasting plasma glucose (mg/dl) (P) <0.001 , LR(P)=0.002) and demonstrated a linear increase in HR with admission FPG. However, HbA1c did not show statistical significance in an equally adjusted model and additionally failed the proportional hazards assumption test.

Furthermore, we evaluated several established metrics of variability SD, CoefVar, MSSD, rMSSD and DGV of FPG as continuous parameters of FPG variability in multivariable Cox-PH models. While these models include age, sex and history of T2D as a covariate for adjustment, neither were statistically significant in any of the models. Out of these variability metrics, we selected the statistically significant metric with the highest C-Index and lowest AIC, where median DGV outperformed all the other contenders (Supplement Fig. 1).

We created an age and sex adjusted Cox-PH model (LR(P) <0.001) to demonstrate the change of HR by the range of DGV values. In this model, age and sex were not statistically significant (HR: 1.01 [95% CI, 0.99-1.04], P=0.3; HR: 0.94 [95% CI, 0.51-1.71], P=0.833, respectively) in contrast to DGV (HR: 1.02 [95% CI, 1.02-1.03], P <0.001). The model demonstrated a proportional increase in HR and at HR=1 DGV was 34.63mg/dl in males and 27.35 mg/dl in females (Fig. 1).

To determine an outcome-based cut-off for DGV we fitted a regression tree model (25.5 mg/dl) and compared it to a cut-off based on a hazard ratio of 1 derived from a Cox-PH model which was adjusted for age, sex and history of T2D (31 mg/dl). The regression tree-based cut-off demonstrated a higher AUC (0.729 vs. 0.689) in 30-day survival ROC curves, therefore we used the cut-off DGV value of 25.5 mg/dl in further models and testing rather than the Cox-PH based cut-off of DGV 31 mg/dl. In the group with DGV < 25.5 mg/dl (low DGV group), significantly more patients (n=41 (69%)) survived to discharge compared to only 12 patients (25%) with DGV ≥ 25.5 mg/dl (high DGV group) (Table 1). Furthermore, we analysed differences in clinical characteristics, comorbidities, laboratory parameters and medication on admission of patients in high and low DGV groups. There was no significant difference in age, gender, P/F ratio and likelihood of dialysis, ECMO and dexamethasone therapy among both groups. Similarly, there were no statistically significant differences in symptoms reported at or prior to admission between both groups. However, patients in high DGV group were significantly more obese (Median [IQR]: 28.4 [26.3–31.1] vs. 31.2 [27.5–38.1], P=0.01) and had a lower fever at admission to the ICU (Median [IQR]: 38.1 [37.3–38.6] vs. 37.6 [36.9–38.1], P <0.05). Comparing inflammatory markers on admission to the ICU, we found

ferritin to be significantly lower in the high DGV group, whereas leukocytes, lymphocytes, CRP, procalcitonin and IL-6 remained not significantly different between the two groups (Table 1).

Additionally, Kaplan-Meier estimators showed a significantly ($P < 0.0001$) longer median survival of patients in low DGV group of 87 days in comparison to patients in high DGV group, which had a median survival of 25 days (Fig. 2).

Based on these findings, we generated an unadjusted Cox-PH model for mortality in DGV (HR: 1.02, ($P < 0.001$, LR($P < 0.001$)). This model was still significant after adjusting for clinically predetermined confounders (HR: 1.016, ($P = 0.001$, LR($P < 0.001$)). This model demonstrated that median DGV remained independently associated with adverse outcome (Fig. 3).

In order to examine a potentially predictive use of median DGV, we calculated median DGV for the first three days of ICU admission. The results of an equally adjusted model (using the three-day median FPG instead of the median FPG over the entire ICU admission) indicated nonetheless significant association of three-day median DGV with adverse outcome (Supplement Fig. 2).

Discussion

To our knowledge, this is the first study to provide direct evidence that higher glucose variability is associated with higher mortality in COVID-19 patients with ARDS.

Previous cohorts in China, Germany, France, Italy, and the US have already established the high prevalence of T2D^{5,8-11} among COVID-19 patients admitted to the hospital. Even though prior diagnosis of T2D certainly predisposes patients for hyperglycemia, a recent review¹² identified hyperglycemia in up to 40% of ICU patients, where an estimated 80% of patients with hyperglycemia had no prior diagnosis of T2D. We found a similar prevalence of hyperglycemia in our study, albeit history of T2D was equally distributed in patients with hyperglycemia.

Moreover, the CORONADO study⁵ previously reported that HbA1c levels on admission in patients hospitalised for COVID-19 was not associated with adverse outcome. Similarly, a meta-analysis¹³ did not find a statistically significant association between HbA1c and disease severity. Our data reinforces this finding in patients admitted with ARDS to the ICU and augments that high FPG at ICU admission and high FPG variability increase mortality risk in COVID-19 patients admitted with ARDS.

With respect to COVID-19, several early studies identified hyperglycemia as a relevant factor for adverse outcome. Higher FPG levels at admission¹⁴ as well as at day 2-3 of admission¹⁵ and higher glycemic range between FPG and two-hour postprandial glucose¹⁶ have been considered as relevant predictors for fatal outcome.

Furthermore, a recent review¹⁷ of twelve studies regarding the association of elevated FPG and adverse outcome in hospitalised COVID-19 patients concluded that impaired glucose homeostasis appears to be

a common and relevant factor of adverse outcome. They explored several possible underlying molecular mechanisms of disease progression mediated by elevated serum FPG and suggested the increase of glucose concentrations in the alveolar surface liquid to have adverse effects on immune defence against pathogens.

As far as we know, there have been no studies, which explored a possible association between glycemic variability and mortality outcome in COVID-19 patients with ARDS. Therefore, we evaluated several metrics of glycemic variability and concluded that median DGV, even after adjustment for confounders, to be a significant metric in patients with adverse outcome. This effect persists in a predictive model calculated over the first three days of admission.

The present study shows that high variability of FPG, not HbA1c, is significantly associated with an increased risk of all-cause mortality in severely ill COVID-19 patients with ARDS. This effect appears to be independent of clinically predetermined confounders and warrants further research in order to assess the predictive value of glycemic variability. These findings further emphasize the significance of monitoring FPG variability (DGV) in patients admitted to the ICU.

Materials And Methods

Study population

Patients with COVID-19 who were admitted to University Hospital Aachen, Germany, could participate in the prospective retrospective single-centre cohort study, COVAS. The first 125 patients have been previously reported^{18,19}. The present study comprises 106 COVID-19 patients with ARDS who were admitted to the ICU from February 24, 2020, until May 15, 2021. Inclusion criteria were a positive respiratory SARS-CoV-2 PCR result and admission to the ICU requiring mechanical ventilation due to COVID-19 and ARDS.

Since University Hospital Aachen is designated a tertiary care facility, patients with minor or mild severity were triaged by the emergency services towards other regional hospitals. Thus, the present study includes a significant number of patients with severe clinical course from other regional hospitals, who were either previously screened for ECMO or other high-end treatment methods.

All patients gave their written informed consent before participating in this study, which complies with the Declaration of Helsinki. Study approval was acquired by the ethics committee at the Faculty of Medicine of RWTH Aachen University (EK080/20). This trial has been retrospectively registered in the German Clinical Trials Register (DRKS00027106).

Definitions of study parameters

ARDS was defined according to the Berlin definition²⁰. Comorbidities were defined as conditions that were known before hospital admission. Similarly, previous medication included any medication

prescribed before admission to our hospital.

Baseline vital parameters are characterized as the first available measurements after ICU admission. Respiratory disease was defined as a composite of bronchial asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome and pulmonary malignancy. Moreover, composite heart disease is a composite of arterial hypertension, atrial fibrillation, coronary artery disease, heart failure and previous myocardial infarction. History of T2D was specified either by a previously known T2D diagnosis, diabetes medication at time of hospital admission or HbA1c at admission of $\geq 6.5\%$ (48 mmol/mol).

In order to select a suitable metric to evaluate fasting plasma glucose variability, we first compared established parameters: standard deviation (SD), Neuman's (root) mean square of successive differences (MSSD and rMSSD), bias corrected coefficient of variation (CoefVar) and median of the absolute difference between successive values (DGV, daily glucose variance). The median of DGV was computed as follows (Equation 1):

$$DGV_{day} = \left| FPG_{day} - FPG_{day+1} \right|$$

We excluded patients who did not have FPG levels on at least three consecutive days at any point during their ICU admission. This allowed us to identify patients with tighter, both intrinsic and iatrogenic, glucose variability independently of T2D status and glucose lowering treatment. All patients were titrated to a FPG target of 150 mg/dl by means of continuous insulin infusion during ICU admission.

Data acquisition

We collected symptoms on admission, co-morbidities and previous medication either per interview/questionnaire in alert patients or per admission/discharge documents from our emergency department and previous hospitals. Vital parameters were acquired immediately on the first day of ICU admission. On subsequent days, we recorded the worst daily value, in the context of shock and/or respiratory failure. In order to reduce confounders in ventilation parameters, we intentionally omitted the first four hours of ventilation parameters after admission and intubation in order to allow the staff to properly configure the ventilator according to the patient's requirements at the time.

PCR results were acquired by quantitative real-time polymerase-chain-reaction (PCR). Diagnosis of COVID-19 was established by positive respiratory PCR from either a throat swab or tracheal fluid in awake patients and bronchoalveolar lavage (BAL) in intubated patients. Respiratory PCR was repeated on day 7 and 14 of admission. Additionally, BAL, serum, stool and urine samples were tested for bacterial, fungal and viral pathogens, including *Legionella pneumophila* and *Streptococcus pneumoniae* antigens as well as SARS-CoV-2. All patients received daily routine laboratory tests including glucose levels between 03:00 – 05:00 AM.

Statistical analysis

All statistical analysis was performed in R version 4.1.1²¹ using packages ggplot2 (version 3.3.5)²² for scatter plots, tangram (0.7.1)²³ for tables and Rmarkdown for text. The characteristics were described as median (IQR) for continuous and percentages for categorical variables. Categorical parameters were compared by Fisher's Exact Test and continuous parameters by Kruskal-Wallis test. Statistical significance was determined as a p value below 0.05.

We calculated MSSD and rMSSD using the psych package (version 2.1.6)²⁴ and CoefVar using the implementation provided by the DescTools package (version 0.99.43)²⁵.

The cutoff DGV was estimated by regression tree analysis using rpart (version 4.1.15)²⁶. Through rms (version 6.2.0)²⁷, smooth hazard ratios and survival analysis was examined in Cox-proportional-hazard (Cox-PH) models, which were compared by likelihood ratio (LR) test, Akaike information criterion (AIC) and Concordance Index (C-Index). All Cox proportional hazard regression models were tested for the proportional hazard assumption. Prior to analysis and based on clinical judgement, we selected the following confounders for adjustment of our final Cox-PH models: age, sex, BMI, history of type 2 diabetes, dialysis during admission, dexamethasone treatment, median procalcitonine and fasting plasma glucose during ICU admission. Goodness-of-fit calculation for our outcome-based cut-offs were compared by calculating the AUC in 30-day survival models using the implementation of survivalROC (version 1.0.3)²⁸. Utilizing survminer's (version 0.4.9)²⁹ ggforest function, forest plots were created. Furthermore, Kaplan-Meier estimator was calculated with the survival (3.2.13)³⁰ and plotted with the survminer (0.4.9)²⁹ package.

Abbreviations

AFib: Atrial fibrillation

AIC: Aikken Information Criteria

ARDS: Acute respiratory distress syndrome

BAL: Bronchoalveolar lavage

C-Index: Concordance Index

CAD: Coronary artery disease

COPD: Chronic obstructive pulmonary disease

COVID-19: Coronavirus disease 2019

Cox-PH: Cox-proportional-hazard model

CRP: C-reactive protein

CT: Computed tomography

CVD: Cardiovascular disease

DGV: Daily glucose variance

ECMO: Extracorporeal membrane oxygenation

FPG: Fasting plasma glucose

HR: Hazard ratio

HTN: Hypertension

ICU: Intensive care unit

IL-6: Interleukin 6

LR: Likelihood ratio

MI: Myocardial infarction

OSAS: Obstructive sleep apnoea syndrome

P/F ratio: Horowitz index

PCR: Polymerase-chain-reaction

PCT: Procalcitonin

SARS-CoV-2: Severe acute respiratory distress syndrome coronavirus 2

sIL2-R: soluble interleukin 2 receptor

T2D: Type 2 Diabetes Mellitus

TNFalpha: Tumor necrosis factor alpha

Declarations

Funding. This analysis was funded by the University Hospital and Medical Faculty of the RWTH Aachen. NM is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TRR 219; Project-ID 322900939 [M03, M05]).

Acknowledgements

The authors thank all participating patients and the healthcare personnel involved in their care for their tireless effort in both stemming the COVID pandemic, as well as ensuring the success of the ongoing research effort in understanding this disease.

We specifically thank the ICU teams (IM18, OIM2, OIM3), pulmonary isolation ward (IM13) and our Centre for Clinical Studies: Zakiya Coenen-Basmadjie, Merite Emrulai, Gaby Heuer, Hedwig Reichardt, and Mareike Wienands.

We wish all patients a speedy recovery and a quick return to their normal daily lives.

Authors' contributions

BH wrote the manuscript and performed the statistical analysis. MD, NM and DMW designed the study. PB, BH and NH collected the research data. JB, MD, MJ, NM, DMW, PB, NH and MV reviewed/edited the manuscript. NK and DH reviewed and validated the statistical analysis. DMW is the guarantor of this work and had full access to all the data in the study as well as takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate. Study approval was acquired by the ethics committee at the Faculty of Medicine of RWTH Aachen University (EK080/20). The present research complies with the Declaration of Helsinki.

Consent for publication. Not applicable.

Availability of data and materials. *The data underlying this article will be shared on reasonable request to the corresponding author.*

Competing interests. No potential conflicts of interest relevant to this article were reported.

References

1. Hasan SS, Capstick T, Ahmed R, et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. *Expert Review of Respiratory Medicine*. 2020;14(11):1149–1163. doi:10.1080/17476348.2020.1804365
2. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 2020;382(18):1708–1720. doi:10.1056/nejmoa2002032
3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061. doi:10.1001/jama.2020.1585
4. Coppelli A, Giannarelli R, Aragona M, et al. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: The pisa COVID-19 study. *Diabetes Care*. Published online 2020. doi:10.2337/dc20-1380

5. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia*. 2020;63(8):1500–1515. doi:10.1007/s00125-020-05180-x
6. Chen L, Sun W, Liu Y, et al. Association of Early-Phase In-Hospital Glycemic Fluctuation With Mortality in Adult Patients With Coronavirus Disease 2019. *Diabetes Care*. 2021;44(4):865–873. doi:10.2337/dc20-0780
7. Zanella A Florio. Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units. *Intensive Care Medicine*. 2021;47(9):995–1008. doi:10.1007/s00134-021-06495-y
8. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91–95. doi:10.1016/j.ijid.2020.03.017
9. Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 german hospitals: An observational study. *Lancet Respir Med*. Published online 2020. doi:10.1016/S2213-2600(20)30316-7
10. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. *JAMA*. Published online 2020. doi:10.1001/jama.2020.5394
11. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. *Lancet*. 2020;395(10239):1763–1770. doi:10.1016/S0140-6736(20)31189-2
12. Farrokhi F, Smiley D, Umpierrez GE. Glycemic control in non-diabetic critically ill patients. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2011;25(5):813–824. doi:10.1016/j.beem.2011.05.004
13. Chen J, Wu C, Wang X, Yu J, Sun Z. The impact of COVID-19 on blood glucose: A systematic review and meta-analysis. *Frontiers in Endocrinology*. 2020;11. doi:10.3389/fendo.2020.574541
14. Sardu C, D’Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: Can we do more on glycemic control? *Diabetes Care*. 2020;43(7):1408–1415. doi:10.2337/dc20-0723
15. Klonoff DC, Messler JC, Umpierrez GE, et al. Association between achieving inpatient glycemic control and clinical outcomes in hospitalized patients with COVID-19: A multicenter, retrospective hospital-based analysis. *Diabetes care*. 2021;44(2). doi:10.2337/dc20-1857
16. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab*. 2020;31(6):1068-1077 e3. doi:10.1016/j.cmet.2020.04.021
17. Logette E, Lorin C, Favreau C, et al. A machine-generated view of the role of blood glucose levels in the severity of COVID-19. *Frontiers in Public Health*. 2021;9. doi:10.3389/fpubh.2021.695139

18. Dreher M, Kersten A, Bickenbach J, et al. The Characteristics of 50 Hospitalized COVID-19 Patients With and Without ARDS. *Deutsches Aerzteblatt Online*. Published online April 17, 2020. doi:10.3238/arztebl.2020.0271
19. Balfanz P, Hartmann B, Müller-Wieland D, et al. Early risk markers for severe clinical course and fatal outcome in German patients with COVID-19. Cheungpasitporn W, ed. *PLOS ONE*. 2021;16(1):e0246182. doi:10.1371/journal.pone.0246182
20. Acute Respiratory Distress Syndrome. *JAMA*. 2012;307(23). doi:10.1001/jama.2012.5669
21. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2020. <https://www.R-project.org/>
22. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York; 2016. <https://ggplot2.tidyverse.org>
23. Garbett S. *Tangram: The Grammar of Tables*; 2020. <https://CRAN.R-project.org/package=tangram>
24. Revelle W. *Psych: Procedures for Psychological, Psychometric, and Personality Research*. Northwestern University; 2021. <https://CRAN.R-project.org/package=psych>
25. Andri et mult. al. S. *DescTools: Tools for Descriptive Statistics*; 2021. <https://cran.r-project.org/package=DescTools>
26. Therneau T, Atkinson B. *Rpart: Recursive Partitioning and Regression Trees*; 2019. <https://CRAN.R-project.org/package=rpart>
27. Harrell Jr FE. *Rms: Regression Modeling Strategies*; 2020. <https://CRAN.R-project.org/package=rms>
28. Heagerty PJ, Paramita Saha-Chaudhuri packaging by. *survivalROC: Time-Dependent ROC Curve Estimation from Censored Survival Data*; 2013. <https://CRAN.R-project.org/package=survivalROC>
29. Kassambara A, Kosinski M, Biecek P. *Survminer: Drawing Survival Curves Using 'Ggplot2'*; 2020. <http://www.sthda.com/english/rpkgs/survminer/>
30. Therneau TM. *A Package for Survival Analysis in r*; 2020. <https://CRAN.R-project.org/package=survival>

Table

Table 1: Characteristics of patients admitted with COVID-19 and ARDS to the Intensive Care Unit

	N	Overall	DGV<25.5mg/dl	DGV>=25.5mg/dl	P value
		(N=106)	(N=59)	(N=47)	
Age (years)	106	63.0 (57.0–71.0)	62.0 (55.3–69.0)	65.0 (58.2–72.8)	0.12
Sex: female	106	34 (32.1%)	18 (30.5%)	16 (34.0%)	0.83
Endpoint at close-out: Survivor	106	53 (50.0%)	41 (69.5%)	12 (25.5%)	<0.01
Systolic blood pressure (mmHg)	106	97.0 (84.0–104.0)	100.0 (87.2–105.8)	94.0 (83.0–101.8)	0.09
Diastolic blood pressure (mmHg)	106	51.5 (44.0–60.0)	54.0 (45.0–61.0)	49.0 (42.2–56.7)	0.05
Heart rate (1/min)	106	100.5 (86.0–116.0)	98.0 (84.3–112.8)	102.0 (90.3–118.0)	0.21
Temperature (°C)	106	37.8 (37.2–38.4)	38.1 (37.3–38.6)	37.6 (36.9–38.1)	<0.05
Highest Respiratory Rate (1/min)	104	26.0 (22.0–29.6)	26.0 (22.0–30.0)	25.0 (21.0–27.3)	0.40
arterial oxygen saturation (%)	95	94.6 (90.9–96.9)	94.5 (91.3–96.7)	94.9 (90.2–97.5)	0.57
Lowest P/F ratio	103	112.0 (86.2–148.0)	107.5 (85.9–145.1)	117.0 (87.0–163.7)	0.25
BMI (kg/m ²)	106	29.4 (26.3–33.8)	28.4 (26.3–31.1)	31.2 (27.5–38.1)	0.01
ECMO therapy	106	30 (28.3%)	18 (30.5%)	12 (25.5%)	0.67
Dialysis	106	70 (66.0%)	34 (57.6%)	36 (76.6%)	0.06
Dexamethasone	106	43 (40.6%)	23 (39.0%)	20 (42.6%)	0.84
Composite respiratory disease	106	33 (31.1%)	17 (28.8%)	16 (34.0%)	0.67
Composite heart disease	106	34 (32.1%)	13 (22.0%)	21 (44.7%)	0.02
Hypertension	106	69 (65.1%)	34 (57.6%)	35 (74.5%)	0.10
Atrial fibrillation	106	13 (12.3%)	4 (6.8%)	9 (19.1%)	0.07
Coronary artery disease	106	25 (23.6%)	10 (16.9%)	15 (31.9%)	0.11
Myocardial infarction	106	15 (14.2%)	6 (10.2%)	9 (19.1%)	0.26
Fasting plasma	106	144.0 (116.0–	133.0 (106.2–	167.0 (131.3–	<0.01

glucose (mg/dl)		189.1)	161.7)	224.3)	
Glucose, median* (mg/dl)	106	149.2 (135.0–168.1)	141.5 (129.0–151.8)	168.0 (148.9–186.8)	<0.01
FPG, 3-day median* (mg/dl)	106	155.0 (138.0–193.1)	146.0 (129.8–169.0)	185.5 (148.9–210.2)	<0.01
DGV, median* (mg/dl)	106	22.5 (15.9–33.0)	16.0 (13.0–20.0)	35.0 (29.5–52.3)	<0.01
DGV, 3-day median* (mg/dl)	106	31.0 (16.0–55.1)	22.0 (13.2–31.8)	42.0 (32.2–93.5)	<0.01
HbA1c (%)	87	6.1 (5.7–6.6)	6.0 (5.5–6.2)	6.4 (5.9–7.2)	<0.01
Leukocytes (/μl)	106	10.0 (7.4–13.6)	10.0 (7.7–13.5)	9.7 (7.1–14.5)	0.96
Lymphocytes (/μl)	90	0.7 (0.3–1.1)	0.7 (0.3–1.1)	0.7 (0.5–1.0)	0.92
D-dimer (μg/l)	79	2252.0 (1237.8–7168.5)	3525.0 (1389.5–7244.5)	1614.5 (755.6–5688.1)	0.09
Ferritin (ng/ml)	56	1389.5 (823.9–2641.0)	1690.0 (1054.0–2792.7)	1020.5 (662.2–2057.8)	<0.05
CRP (high-sense) (mg/l)	97	169.0 (113.6–287.3)	172.7 (131.4–275.4)	160.0 (86.8–300.7)	0.50
Procalcitonin (ng/ml)	106	0.5 (0.2–1.7)	0.4 (0.2–1.2)	0.6 (0.2–1.9)	0.31
Procalcitonin, median* (ng/ml)	106	0.8 (0.3–2.6)	0.5 (0.2–1.5)	1.5 (0.6–4.5)	<0.01
IL-6 (pg/ml)	84	142.9 (77.9–325.5)	133.1 (67.0–338.0)	160.9 (95.1–294.3)	0.54

Numerical parameters are expressed as median(IQR) and categorical as N(%). The N column represents the number of non-missing values in each row to the right. P-values for differences between the two groups were tested using Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Bold indicates significant differences (P<0.05). Parameters denoted with * are calculated over the first three days("3-day") or entire course of ICU admission. Composite heart disease is defined as atrial fibrillation, coronary artery disease, hypertension, heart failure or history of myocardial infarction. Composite respiratory disease was defined as a composite of bronchial asthma, chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome and pulmonary malignancy.

Figures

Figure 1

Relation between fatality risk and glucose variability

Continuous hazard ratios for fatality or non-survival were calculated by Cox proportional hazard models of daily glucose variance (DGV) adjusted for age and sex, including 95% CI for endpoint. The dashed red line notates a hazard ratio of 1.0, the solid black line the dichotomisation threshold, which we determined using a regression tree. The threshold of 25.5mg/dl for DGV was used for our summary statistics (Table 1), Kaplan-Meier curves (Fig. 2) and the adjusted DGV Cox proportional hazard model (Fig. 3).

Figure 2

Kaplan-Meier Survival for ARDS Patients

Kaplan-Meier survival curves for patients with low ($<25.5\text{mg/dl}$) and high ($\geq 25.5\text{mg/dl}$) daily glucose variance (DGV). Each cross on a curve represents a censored patient (survived to discharge), while each step in the curve represents a deceased patient. The x-axis represents the time in days to discharge.

Figure 3

Adjusted hazard ratios for non-survival by DGV

Multivariable Cox proportional hazard model for median daily glucose variance (DGV) cut-off as a continuous covariate dichotomised at $\text{DGV} \geq 25.5\text{mg/dl}$, adjusted for clinically predetermined confounders: age, sex, BMI, type 2 diabetes status, dialysis, dexamethasone treatment, median of procalcitonine, glucose and DGV during ICU admission.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFigure1.tiff](#)
- [SupplementalFigure2.tiff](#)