Insulin sensitivity and blood glucose level analysis of critically ill patients in their early phase of ICU treatment

Anane Yahia[1], Balazs Benyo[1], J. Geoffrey Chase [2]

[1] *Budapest University of Technology and Economics, Department of Control Engineering and Information Technology, Budapest, Hungary;* yahiaanane@iit.bme.hu, bbenyo@iit.bme.hu

[2] *Mechanical Engineering, Centre of Bio-Engineering, University of Canterbury, Christchurch, NZ;* geoff.chase@canterbury.ac.nz

Abstract: **Critically ill intensive care unit (ICU) patients frequently experience acute insulin resistance (low insulin sensitivity) manifesting as stress-induced hyperglycemia and hyperinsulinemia, especially in the early stages of the treatment. High inter/intra-patient variability makes glycemic control difficult. Stochastic TARgeted (STAR) a model-based glycemic control, directly manages this variability using model-based insulin sensitivity (SI) and a second model of its variability. Early occurrence of insulin resistance and hyperglycemia may need a special (customized) model-based control designed only for the early phase of patient treatment. This study analyses insulin sensitivity and blood glucose levels of ICU patients from 3 different cohorts and compares the first 24h of the treatment and the rest of the treatment in order to assess the differences. Using clinical data from 717 patients treated with STAR in three independent cohorts (Hungary, New Zealand, and Malaysia), insulin sensitivity and blood glucose are compared at first between the first 24h and the rest of the treatment, then the first 24h and the successive treatment days. Results show that insulin sensitivity is lower in the first 24h compared to the rest of the treatment and in the first 24h compared to the five successive days. The differences were noticeable in the Hungarian and New Zealand cohort but not for the Malaysian cohort. Blood glucose levels were higher in all cohorts in the first 24h compared to the rest of the treatment time and in the first 24h compared to the five successive days. Patients in the early stages of ICU have low insulin sensitivity and high blood glucose levels, as expected, given the stress response physiology. Given the results, this study initiates the idea of Implementing a customized model-based control designed only for the early phase of patient treatment that can effectively handle patients' hyperglycemia and insulin resistance and create a space for further development.**

Keywords: Blood glucose; Glycemic control; STAR; Insulin resistance; Insulin sensitivity; ICU.

Introduction

Effective glycemic control showed a promising improvement in the outcomes in critically ill patients. However, it was always hard to achieve consistent results [1] due to patients' intra-and-inter variability.

Patients in their early stage of treatment after ICU admission due to stress often experience insulin resistance (low insulin sensitivity), resulting in high blood glucose levels (hyperglycemia), making glycemic control very sensitive in the intensive care unit [2].

In this paper, we used patient data of 717 patients from 3 different Hospitals' ICUs: New Zeeland, Malaysia, and Hungary treated by STAR protocol. Stochastic TARgeted (STAR) is a Glycemic control protocol that models patient-specific intra-and-inter variability [3]. STAR is driven by a model-based, insulin sensitivity (SI) used as a key parameter to assess the patient variability. It is built on the clinically validated Intensive Control Insulin- Nutrition-Glucose (ICING) model used to characterize the fundamental Glucose-Insulin system dynamics.

We analyzed patients insulin sensitivity and blood glucose levels across the different cohorts, and the aim of this work is to examine the inter/intra differences in insulin sensitivity and hyperglycemia in the early stages of the treatment (first 24h hours of patient ICU admission) compared to the rest of the treatment time and its potential impact on model-based glycemic control.

This study initiates the idea of implementing a customized model-based control explicitly designed for the early phase of patient treatment that can effectively handle patients' hyperglycemia and insulin resistance.

Methods

STAR protocol

STAR utilizes the Intensive Care Insulin-Nutrition-Glucose (ICING) model to simulate the fundamental metabolic dynamics of the glucose/insulin system of the human body [4]. The main 3 of 7 total equations are defined:

$$\dot{G} = -p_G G(t) - SI * G(t)\frac{Q(t)}{1 + a_G Q(t)} + \frac{P(t) + EGP - CNS}{V_G} \quad (1)$$

$$\dot{I} = -n_k I(t) - n_L \frac{I(t)}{1 + a_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}(t)}{V_I} + (1 - x_L)\frac{u_{en}(G)}{V_I} \quad (2)$$

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + a_G Q(t)} \quad (3)$$

The model parameters, the inputs variables, and their detailed description can be found in [4].

Patient data

Clinical data that contains a patient's personal information, blood glucose measurements, and insulin/nutrition treatment was collected from 3 different cohorts of 717 ICU patients.

216 from the International Islamic University Malaysia Medical Centre, Malaysia, 408 from Christchurch Hospital, New Zeeland, 93 patients from Kalman Pandy Hospital, Gyula, Hungary [5].

Insulin sensitivity

Insulin sensitivity (SI), the primary key parameters uniquely identified from clinical data on an hourly basis and patient variability is assessed by the hour-to-hour change in SI levels. Low values of SI indicate insulin resistance and the need to either add insulin or reduce nutrition to achieve lower glycemic levels.

Clinical data including two last BG measurements, insulin/nutrition inputs, and ICING model Equations (1)-(7) is utilized to identify SI on hourly bases using the integral-based method [6].

Analysis

We analyzed the patient's inter-intra cohort insulin sensitivity identified by STAR and the measured blood glucose levels during the treatment across the different cohorts. First, we compared values between the first 24h and the rest of the treatment time. Second, we compared values between the first 24h and the next four successive treatment days. We also analyzed Episodes of Insulin resistance (SI<10-5 L/mU/min) and Episodes of hyperglycemia (BG>10 mmol/l). For the second part, we exclude patients with a treatment time record of less than 120 hours.

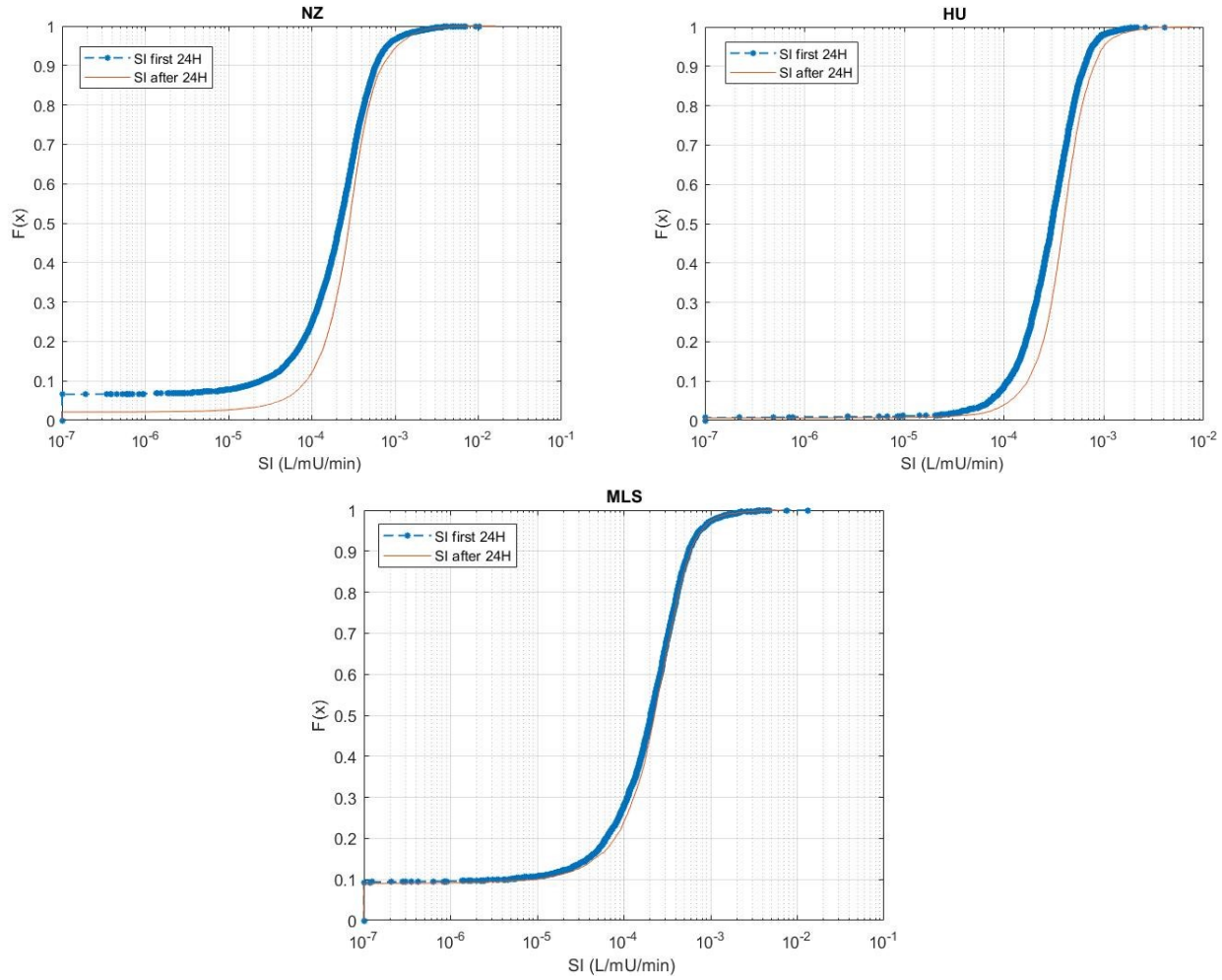
Results

Insulin sensitivity

SI in the first 24h vs. the rest of the treatment

Figure 1 shows the cumulative distribution function of insulin sensitivity (SI) of all patients under the New Zeeland, Hungarian and Malaysian cohort in the first 24h compared to the SI in the rest of the treatment time. Inter-cohort SI values are lower in the first 24h compared to the rest of the treatment. The differences were noticeable in the Hungarian and New Zealand cohort with mean values of 3.06 10^{-4} and 3.51 10^{-4} in the first 24h compared to 3.84 and 4.64 after, but not for the Malaysian cohort where the difference is small (2.04 10^{-4} and 2.25 10^{-4}) as seen in Table 1.

Intra-cohort Si values also vary, with the Malaysian cohort having the lowest SI values and the Hungarian cohort being the highest. The Min value of SI is 10-7 in all cohorts, which is the minimum physiological allowed value in the STAR protocol during the SI identification phase.



1. Figure: Cdf of SI values in the first 24h compared to SI in the rest of the treatment for the 3 cohorts.

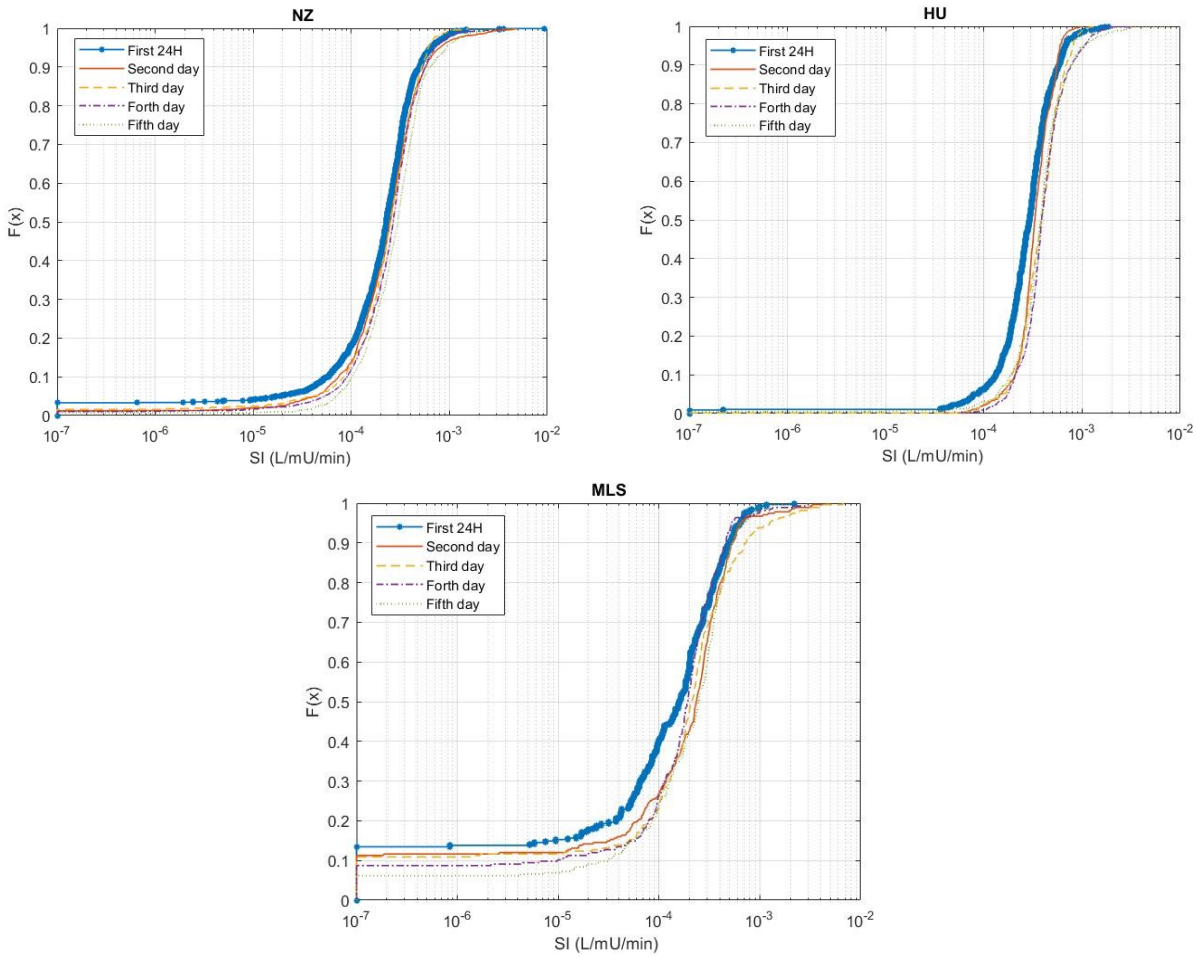
1. TABLE: SI VALUES COMPARISON IN THE FIRST 24H VS. REST OF THE TREATMENT FOR THE 3 COHORTS

Stats	Cohorts					
	NZ		HU		MLS	
	First 24h	*After 24h*	*First 24h*	*After 24h*	*First 24h*	*After 24h*
MIN	10^{-7}	10^{-7}	10^{-7}	10^{-7}	10^{-7}	10^{-7}
MAX	$1.03\ 10^{-2}$	$1.63\ 10^{-2}$	$0.41\ 10^{-2}$	$0.76\ 10^{-2}$	$1.34\ 10^{-2}$	$0.37\ 10^{-2}$
MEAN	$3.06\ 10^{-4}$	$3.84\ 10^{-4}$	$3.51\ 10^{-4}$	$4.64\ 10^{-4}$	$2.83\ 10^{-4}$	$2.97\ 10^{-4}$
MEDIAN	$2.17\ 10^{-4}$	$2.82\ 10^{-4}$	$3.01\ 10^{-4}$	$3.91\ 10^{-4}$	$2.04\ 10^{-4}$	$2.25\ 10^{-4}$

SI in the first 24h vs. next four days

Figure 2 shows the cumulative distribution function of insulin sensitivity (SI) of all patients under the New Zeeland, Hungarian and Malaysian cohorts in the first 24h compared to SI in the four successive treatment days. Based on SI mean values reported in Table 2, the lowest value was at the first 24h compared to the next four days of the treatment in all the three different cohorts, as low as $2.13\ 10^{-4}$ in the MLS cohort, $2.73\ 10^{-4}$ in the NZ cohort and $3.29\ 10^{-4}$ in the HU cohort. The mean values go up on the 2nd day in all cohorts.

Episodes of Insulin resistance (%IR) are higher in the first 24h compared to the four successive days. The Hungarian cohort has the lowest insulin resistance episodes of 1.07%, and the Malaysian cohort has the highest of 15.27%



2. Figure: Cdf SI values in the first 24h compared to the next four days for all cohorts.

2. TABLE: SI VALUES COMPARISON BETWEEN THE FIRST FIVE DAYS OF TREATMENT FOR THE 3 COHORTS

Time period /Stats	Cohorts					
	NZ		HU		MLS	
	Mean	*% IR*	*Mean*	*% IR*	*Mean*	*% IR*
First 24h	$2.73\ 10^{-4}$	4.16	$3.29\ 10^{-4}$	1.07	$2.13\ 10^{-4}$	15.27
24-48h	$3.33\ 10^{-4}$	1.92	$3.56\ 10^{-4}$	0	$3.04\ 10^{-4}$	12.00
48-72h	$2.84\ 10^{-4}$	2.40	$4.16\ 10^{-4}$	0.15	$3.72\ 10^{-4}$	11.63
72-96h	$3.20\ 10^{-4}$	1.60	$3.62\ 10^{-4}$	0	$2.48\ 10^{-4}$	10.18
96-120h	$3.65\ 10^{-4}$	0.72	$4.71\ 10^{-4}$	0.61	$2.79\ 10^{-4}$	6.90

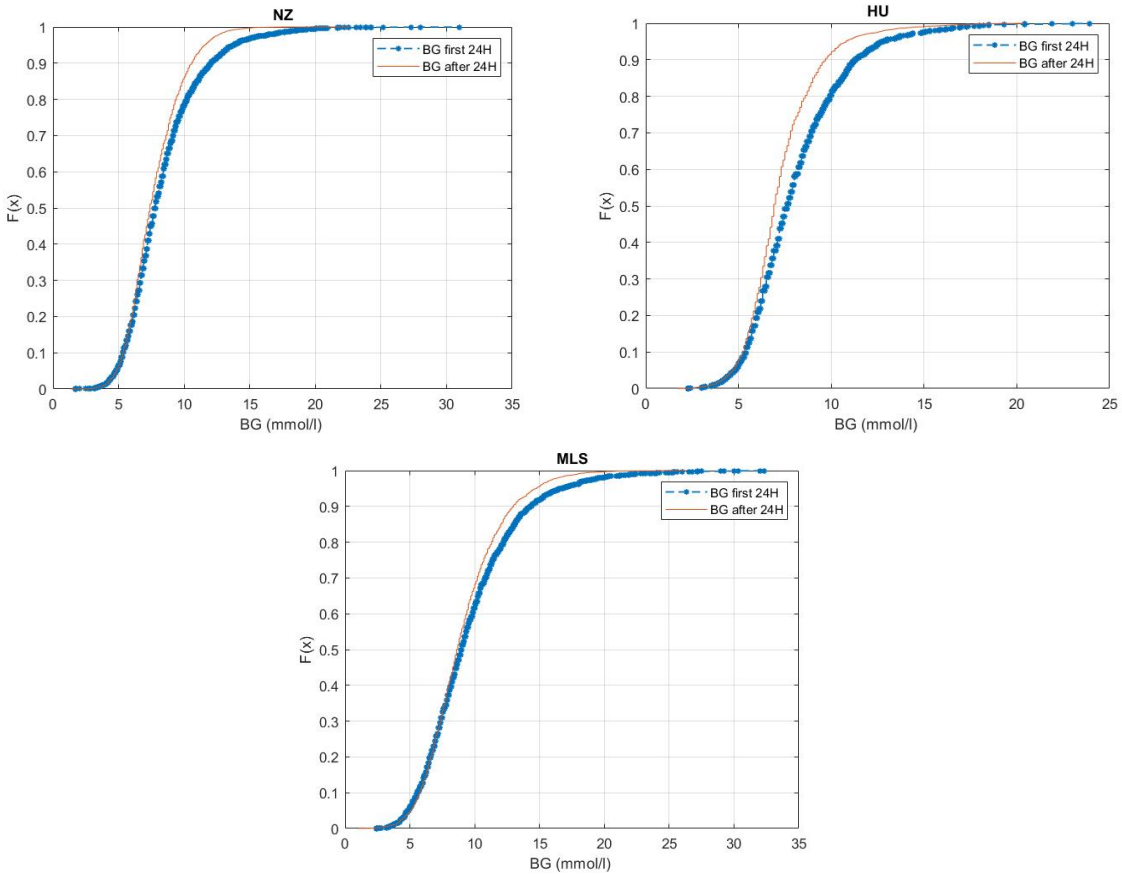
Blood glucose

BG in the first 24h vs. rest of the treatment

Figure 3 shows the cumulative distribution function of blood glucose measurements (BG) of all patients under the New Zeeland, Hungarian and Malaysian cohort in the first 24h compared to the BG in the rest of the treatment time. Inter-cohort BG values are higher in the first 24h compared to the rest of the treatment. The differences were not significant in terms of mean values, which is 0.54-0.81 mmol/l difference between the first 24h and after. However,

there is a noticeable difference in the maximum BG values recorded, in which the difference is up to 8.4 mmol/l, as seen in Table 3.

Intra-cohort BG values also vary, with the Malaysian cohort having the highest BG values and the Hungarian cohort being the lowest.



3. Figure: Cdf of BG values in the first 24h compared to the rest of the treatment for the 3 cohorts.

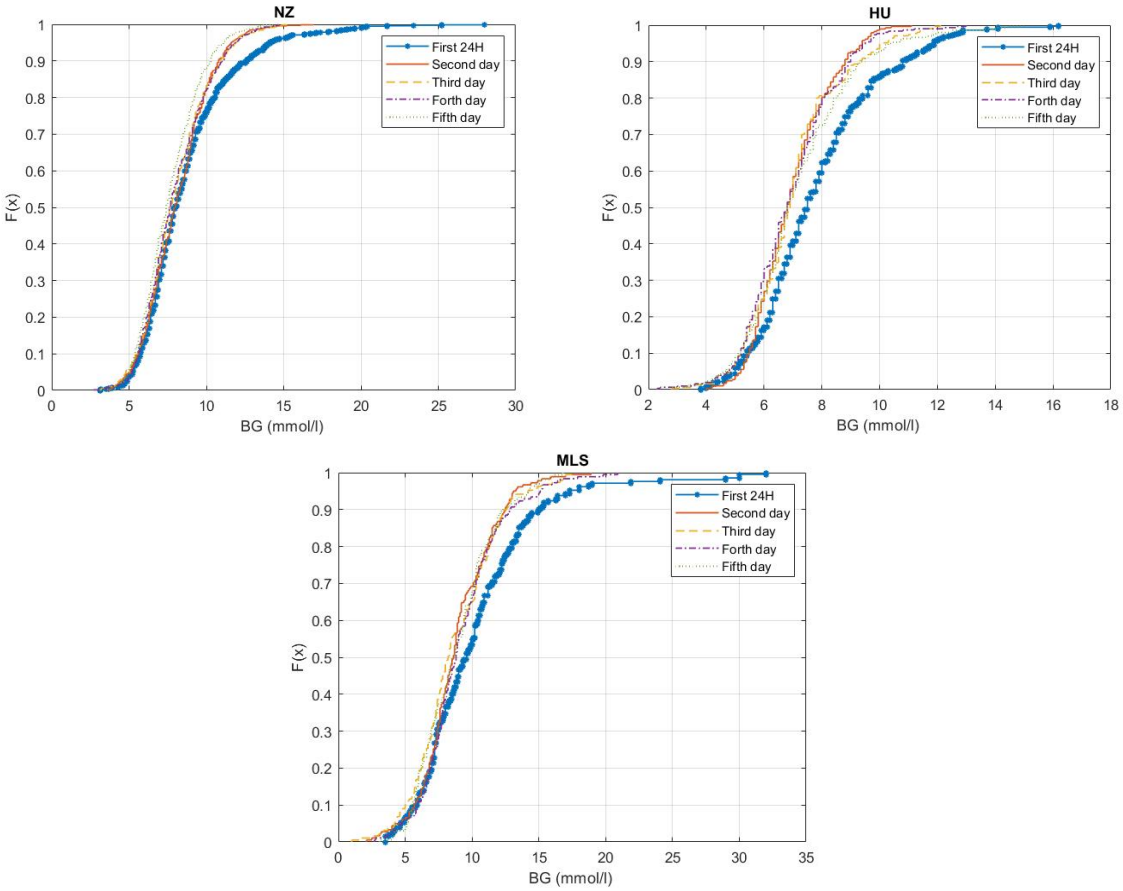
3. TABLE: BG VALUES COMPARISON IN THE FIRST 24H VS. REST OF THE TREATMENT FOR THE 3 COHORTS

Stats	Cohorts					
	NZ		HU		MLS	
	First 24h	*After 24h*	*First 24h*	*After 24h*	*First 24h*	*After 24h*
MIN	1.7	1.3	2.3	1.7	2.4	1
MAX	31	22.6	23.9	20.4	32.30	26.30
MEAN	8.34	7.72	8.09	7.28	9.61	9.07
MEDIAN	7.80	7.40	7.60	6.90	9	8.70

BG in the first 24h vs. next four days

Figure 4 shows the cumulative distribution function of Blood glucose (BG) of all patients under the New Zeeland, Hungarian and Malaysian cohorts in the first 24h compared to SI in the four successive treatment days. Based on BG mean values reported in Table 4, the highest BG mean value was at the first 24h compared to the next four days of the treatment in all the three different cohorts, as high as 10.20 in the MLS cohort. BG values drop on the 2nd day in all cohorts.

Episodes of hyperglycemia (%HG) are higher in the first 24h compared to the four successive days. The Malaysian cohort has the highest hyperglycemia episodes of almost half of the measurements (45.23%), and the Hungarian cohort has the lowest episodes.



4. Figure: Cfd of BG in the first 24h compared to next 4 days of treatment

4. TABLE: BG VALUES COMPARISON BETWEEN THE FIRST 5 DAYS OF TREATMENT FOR THE 3 COHORTS

Time period /Stats	Cohorts					
	NZ		HU		MLS	
	Mean	*%HG*	*Mean*	*%HG*	*Mean*	*%HG*
First 24h	8.68	23.52	7.80	13.85	10.20	45.23
24-48h	8.11	16.68	6.70	1.03	8.82	30.76
48-72h	7.99	16.83	7.00	5.16	8.72	34.92
72-96h	8.00	17.66	6.90	2.28	8.80	33.87
96-120h	7.64	12.00	7.16	7.02	8.60	31.92

DISCUSSION

From the distribution of identified SI values and BG measurements for all 3 cohorts, there were noticeable differences between the first 24h and the successive days until the end of the treatment where the lowest Si values and the highest BG values were always in the first 24h also the proportion of hours of insulin resistance and hyperglycemia. The Hungarian cohort had the highest SI and lowest BG but also had far fewer hours, and thus there may be a bias [7]. However, considering the analysis of the treatment difference, the CHO intake of the Hungarian cohort was significantly higher. On the other hand, the Malaysian cohort had the lowest SI and highest BG levels. These differences may also reflect cohort differences in the incidence of greater complexity and level of critical illness, such as incidence of severe sepsis, in some cohorts, which can occur from the areas and types of patients treated, as well as from treatment selection or treatment failure bias.

Early occurrence of hyperglycemia episodes is likely due to the surge in EGP seen particularly in severe sepsis and septic shock patients in the first 12-24 hours of the stay [8,9]

This behavior matches clinical expectations and is due to stress [10], often seen in the first 24 hours of stay, particularly in severe sepsis and septic shock patients, all of which match the metabolic variability seen in the first 24h of stay. Thus, this phenomenon occurs qualitatively matches broad clinical expectations.

CONCLUSIONS

Patients in the early stages of ICU have low insulin sensitivity and high blood glucose levels, as expected, given the stress response physiology. Results align with the clinical expectations were the lowest insulin sensitivity values and the highest blood glucose levels tend to be in the first 24h in all cohorts. Given the results, this study initiates the idea of implementing a customized model-based control designed explicitly for the early phase of patient treatment, exactly the first 24h that can effectively handle patients' hyperglycemia and insulin resistance. These beneficial impacts may arise for STAR or any other model-based protocol from improved predictions and thus more accurate GC during treatment for early-stage treatments.

ACKNOWLEDGMENTS

Grants supporting the research presented: National Research Development and Innovation Fund, OTKA K116574; TKP2020 BME-Biotechnology FIKP grant of EMMI (BME FIKP-BIO); EU H2020 MSCA-RISE: DCPM (#872488) grant.

REFERENCES

[1] Bagshaw, S. M., R. Bellomo, M. J. Jacka, M. Egi, G. K. Hart and C. George (2009). The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care* **13**(3): R91.

[2] Krinsley, J. S. (2003). Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* **78**(12): 1471-1478.

[3] Evans, A., A. Le Compte, C. S. Tan, L. Ward, J. Steel, C. G. Pretty, S. Penning, F. Suhaimi, G. M. Shaw and T. Desaive (2012). Stochastic Targeted (STAR) Glycemic Control: Design, Safety, and Performance. *Journal of Diabetes Science and Technology* **6**(1): 102-115.

[4] Lin, J., N. N. Razak, C. G. Pretty, A. Le Compte, P. Docherty, J. D. Parente, G. M. Shaw, C. E. Hann and J. Geoffrey Chase (2011). A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients. *Comput Methods Programs Biomed* **102**(2): 192-205.

[5] Stewart, K.W., et al., *Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis.* Ann Intensive Care, 2016. **6**(1): p. 24.

[6] Chase, J.G., et al., *Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them.* Biomed Eng Online, 2018. **17**(1): p. 24.

[7] Shaw, G.M. and J.G. Chase (2012). Does "treatment failure bias" impact comparisons of ICUs? Intensive Care Med, 38(8): p. 1412.

[8] Anane, Y., B. Benyo, A. Szlavecz, C. Pretty and J. G. Chase (2019). Endogenous glucose production parameter estimation for intensive care patients. *2019 Scientific Meeting on Electrical-Electronics & Biomedical Engineering and Computer Science (Ebbt)*: *IEEE*, pp. 1-4.

[9] Thorell, A., O. Rooyackers, P. Myrenfors, M. Soop, J. Nygren and O. H. Ljungqvist (2004). Intensive insulin treatment in critically ill trauma patients normalizes glucose by reducing endogenous glucose production. *J Clin Endocrinol Metab* **89**(11): 5382-5386.

[10] McCowen, K. C., A. Malhotra and B. R. Bistrian (2001). Stress-induced hyperglycemia. *Crit Care Clin* **17**(1): 107-124.