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Model-Based Glycaemic Control in Multicentre ICUs within Diabetic Patients: In-silico Analysis

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Abstract

Sliding-scale insulin therapy has been vastly used for glycaemic control but dysglycaemia remains high. Model-based glycaemic control that incorporates insulin nutrition protocol was proposed as this therapy provides personalized care to avoid dysglycaemia. Thus, this paper aims to implement in-silico simulation and identify which model-based control protocols yield better protocol within ICU diabetic patients based on performance and safety. Multicentre ICU patients of 282 were divided into diabetes mellitus (DM) and non-diabetes mellitus (NDM) cohort where in-silico simulations were done using Specialised Relative Insulin Nutrition Therapy (SPRINT), SPRINT+Glargine and Stochastic Targeted (STAR) protocols. Performance was verified based on the percentage of blood glucose (BG) time in band (TIB) 6.0 – 10.0 mmol/L and safety with number of mild and severe hypoglycaemia episodes. Among the three protocols, STAR protocol showed the highest median and interquartile range % BG TIB 6.0 – 10.0 mmol/L for DM and NDM patients with 71.6 % [57.9 – 79.8] and 77.4 % [62.9 – 88.8]. The number of hypoglycaemia episodes are the lowest in DM and NDM patients too compared to other protocols. These advantages show that STAR protocol can provide better patient outcomes for glycaemic control with personalized care.

1. Introduction

Diabetes mellitus (DM) patients in the intensive care unit (ICU) often encountered challenges with dysglycaemia (hyperglycaemia, hypoglycaemia and glycaemic variability) which may lead to high mortality and morbidity (American Diabetes Association, 2020; Plummer et al., 2016). (Umpierrez et al., 2002) demonstrated that hyperglycaemia occurs in 12% and 26% of the admitted non-diabetes mellitus (NDM) and DM patients, respectively. Hyperglycaemia in critically ill patients has higher endogenous glucose production that is stimulated by the pro- inflammatory response thus increasing insulin resistance (Ichai & Preiser, 2018).

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The association between hyperglycaemia with myocardial infarction and hospital mortality in DM patients were reported in (Capes et al., 2000; Esdaile et al., 2023). This shows that hyperglycaemia for DM patients within ICU had such adverse outcomes when BG control is not efficient or less suitable in DM cohorts. Meanwhile, hypoglycaemia is indicated when patient's BG dropped to less than 2.2 mmol/L (severe) and less than 4.0 mmol/L (mild) which and mostly occur in Type 2 Diabetes Mellitus (T2DM) patients (Dissanayake et al., 2018; Malaysian Endocrine and Metabolic Society (MEMS), 2020). High mortality risk and loss of consciousness are some of the implications that may occur when patients are hypoglycaemic (Graveling & Frier, 2009) which can be worse than hyperglycaemia for ICU DM patients.

Over the years, sliding-scale insulin therapy is used in most government run hospital in Malaysia (Malaysian Society ofIntensive Care, 2012) following the guidelines. Thus, it has become a challenge when changing sliding-scale insulin therapy to an automated personalized care. The ICUs setting with this therapy applied a 'one size fits all' method since the protocol provides a fast decision clinically based on glycaemic control guidelines. Despite immediate treatment is given, the sliding-scale protocol may not necessarily be productive or cost-saving (Amerling et al., 2008; J. Geoffrey Chase et al., 2019) due to different patient's reaction towards the insulin treatment. Furthermore, sliding scale insulin therapy has no combination of nutrition given when insulin was administered continuously that may lead to hypoglycaemia (Zaman et al., 2007; Zaman Huri et al., 2014), and hyperglycaemia with longer length of stay (Umpierrez et al., 2007).

A 'one method fits all' like model-based glycaemic control (J Geoffrey Chase et al., 2005, 2007; James Geoffrey Chase et al., 2006) can improve ICU patient's outcomes such as reduced organ failure (J Geoffrey Chase, Pretty, et al., 2010), hypoglycaemia, and nursing workload (N. N. Razak et al., 2016). Model-based glycaemic control also offers decision care as the protocol relies on metabolic parameter known as insulin sensitivity (S_I) to provide desirable blood glucose (BG) range. This personalized care method can be delivered in an in-silico trial, to provide safe means since BG's outcome and other performances scenarios is virtually identified. Lastly, an effective glycaemic control can provide little or no hypoglycaemia episode, BG concentration with consistent control, shorten the duration in ICU stay, while compliance for nurses is easy without burnout. All of these can be validated through virtual trial.

Virtual trial is an in-silico simulation technique which was developed with model-based glycaemic control and real clinical data for personalized care (J. Geoffrey Chase et al., 2018; J Geoffrey Chase et al., 2018; J Geoffrey Chase et al., 2010) and to test the glycaemic control effectiveness. The virtual trial simulation can assess protocol performance, safety, nursing workload, feeding adjustment even generalizing the control protocol (Dickson et al., 2018; A. A. Razak et al., 2018; Stewart et al., 2017; Uyttendaele et al., 2017). Rapid testing for protocol performance, allow a safe and efficient protocol prior to clinical trials with thorough virtual trial.

There are several protocols that have coupled with model-based control which are, Specialised Relative Insulin Nutrition Therapy (SPRINT) (Benyo et al., 2012; Lonergan et al., 2006a), SPRINT+Glargine (N. N. Razak et al., 2016),and stochastic targeted (STAR) (Fisk et al., 2012) used for glycaemic control. The model-based control protocol performance reported in (Benyo et al., 2012) for % BG within time in band 4.4 – 8.0 mmol/L was 82.9% [67.8–89.0] and compared to (J Geoffrey Chase et al., 2008) with 83.3 % [69.2–91.5]. Meanwhile, Stochastic Targeted (STAR) protocol demonstrated in (Evans et al., 2012; Fisk et al., 2012) assessed %BG TIB 4.0 – 8.0 mmol/L performance which shown to have 90%. Based on these protocols implementation, although STAR was improved based on SPRINT, SPRINT+Glargine was also proposed in this analysis study where this protocol showed to have reduced nursing workload. All of these model-based control protocols have been tested based on different ICU settings and none emphasized the significant differences in which protocol have better performances in the ICU diabetic patients.

Since model-based glycaemic control is a clinical practice change in the ICU setting, it is important to validate and assess how the variations of administered insulin and nutrition in different control protocols will affect patients' and control outcomes. Thus, in these in-silico analysis study, the aim is to identify which model-based control protocols candeliver better efficiency in BG performance and safety in multicentre ICUs for diabetic patients with personalized care.

2. Materials and Method

Table 1 shows 282 retrospective patients data from multicentre ICUs from three hospitals which are Hospital Tunku Ampuan Afzan (HTAA), Hospital Universiti Sains Malaysia (HUSM), and Universiti Malaya Medical Centre (UMMC) with total length of stay of 32,031 hours. There are 144 non-diabetes mellitus (NDM) patients with longer total ICU stay of 19,329 hours compared to diabetes mellitus (DM) patients with 15,702 hours. The percentage of Malay patients are the highest followed by Chinese and Indian in these three ICUs. The median age and IQR are 58 [46 – 65] for DM and 58 [41 – 66] years old for NDM patients. The age and weight distribution for all patients are almost similar. The median and IQR LOS for DM and NDM patients are 4 [3 – 5] and 5 [3 – 6] days, respectively. Mann- Whitney test was done for age, weight and length of stay in the ICU between both DM and NDM cohorts.

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Amongst 138 DM patients, 22.4% disease diagnosed are related to lungs such as Community-Acquired Pneumonia(CAP). NDM patients had higher patients diagnosed related to sepsis and heart diseases by 23.6% and 12.5% comparedto DM patients. Other diseases such as dengue, trauma also contributed to the diagnosis statistics in DM and NDM.

Table 1 *Patient's demographics*

Demographics	**DM**	**NDM**
Number of patients (%)	138 (48.9%)	144 (51.1%)
Gender [total number (%)]		
• Female	70 (50.7%)	72 (50.0%)
• Male	68 (49.3%)	72 (50.0%)
Ethnicity [total number (%)]:		
• Malay	102 (73.9%)	124 (86.1%)
• Chinese	20 (14.4%)	14 (9.7%)
• Indian	14 (10.1%)	6 (4.2%)
• Others	2 (1.6%)	-
Age (years) in median and [IQR]	58 [46 – 65]	58 [41 – 66]
Weight (kilograms) in median and [IQR]	69 [61– 82]	70 [60 –80]
Length of ICU stay (days) in median and [IQR]	4 [3 – 5]	5 [3 – 6]
Disease related [total number (%)]:		
• Lungs	31 (22.4%)	30 (20.8%)
• Heart	11 (7.9%)	18 (12.5%)
• Kidney	20 (14.4%)	5 (3.6%)
• Brain	8 (6.2%)	12 (8.3%)
• Sepsis	28 (20.2%)	34 (23.6%)
• Others	40 (28.9%)	45 (31.2%)

2.1 Identified Insulin Sensitivity

Patient's insulin sensitivity (S_I) was identified for personalized care. Blood glucose measurements (mmol/L), administered insulin (U/hr), and nutrition infusion (g/hr) were collected based on patient length of stay in the ICU. Before an in-silico trial is simulated, patient data were fitted using clinically validated Intensive Control Insulin Nutrition Glucose (ICING) model (Lin et al., 2011) which implemented an integral fitting method (Hann et al., 2005) to estimate each patient S_I profile. Equations (1) until (7) show the ICING model that was used in this studyas the in-silico modelling approach. Total plasma glucose ($\dot{G}$), total plasma insulin ($\dot{I}$) and total interstitial insulin ($\dot{Q}$) can be identified from Equation (1), (2) and (4). For glucose in the stomach ($\dot{P}_1$), glucose in gut ($\dot{P}_2$) and endogenous of insulin production (u_{en}) were evaluated from Equation (5), (6) and (3) respectively. Table 2 shows the other parameters in ICING model with parameters input implemented from (Lin et al., 2011).

The varying metabolic parameter is represented as S_I for each patient by hourly. Through estimated S_I, patient-specific BG response towards insulin, nutrition given and highly variable of insulin kinetics can be seen.

$$\dot{G} = p_G.G - S_I.G\frac{Q}{1+\alpha_G Q} + \frac{\min(d_2P_2, P_{max}) + EGP_b - CNS + PN}{V_G} \quad (1)$$

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

$$u_{en} = \min(\max(u_{en,min,}, k_1 G + k_2) u_{en,max} \quad (3)$$

$$\dot{Q} = (I - Q) n_I - n_c \frac{Q}{1 + \alpha_G Q} \quad (4)$$

$$\dot{P}_1 = P(t) - d_1 P_1 \quad (5)$$

$$\dot{P}_2 = d_1 P_1 - \min(d_2 P_2, P_{max}) \quad (6)$$

$$\dot{P} = PN(t) - \min(d_2 P_2, P_{max}) \quad (7)$$

Table 2 *Description of ICING model (Lin et al., 2011)*

Symbols (units)	Descriptions	Value
EGP_b (mmol/min)	Basal endogenous glucose production	1.16
CNS (mmol/min)	Glucose uptake by central nervous system	0.3
p_G (min-1)	Endogenous glucose clearance	0.006
S_I (L/mU.min)	Insulin sensitivity	To be identified
V_G (L)	Volume of glucose distribution	13.3
V_I (L)	Volume of insulin distribution	4.0
a_G (L/mU)	Saturation of plasma insulin clearance by liver	1/65
n_L (min-1)	Insulin clearance from plasma via hepatic	0.1578
n_K (min-1)	Insulin clearance from plasma via renal	0.0542
n_I (min-1)	The rate transport between plasma and interstitial insulin compartments	0.006, 0.0075
n_C (min-1)	Cellular insulin clearance rate from interstitium	0.006, 0.0075
x_L (min-1)	1st pass hepatic clearance	0.67
a_I (L/mU)	Insulin dependent glucose clearance	1.7x10-3
d_1 (min-1)	Rate transfer between stomach to gut	-ln(0.5)/20
d_2 (min-1)	Rate transfer from gut to the bloodstream	-ln(0.5)/100
P_{max} (mmol/min)	Maximum disposal rate from the gut	6.11
u_{ex} (mU/min)	Exogenous input insulin	Input data
$u_{en,max}$ (mU/min)	Maximum endogenous insulin production	266.7
$u_{ex,min}$ (mU/min)	Minimum endogenous insulin production	16.7
k_1 (min-1) [NDM, T1DM, T2DM]	Limit of insulin dissociate to plasma	[14.9, 0, 4.9]
k_2 (min-1) [NDM, T1DM, T2DM]	Limit of insulin dissociate to interstitium	[-49.9, 16.7, -27.4]

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2.2 Virtual Trial Analysis

Generated S_I profiles were used as virtual patients for in-silico coupled with three different protocols were run in MATLAB. The three model-based protocols used for glycaemic control were Specialised Relative Insulin Nutrition Therapy (SPRINT) (Lonergan et al., 2006b), SPRINT+ Glargine (N. N. Razak et al., 2016) and Stochastic Targeted (STAR) (Evans et al., 2012; Fisk et al., 2012). SPRINT is a combination of insulin nutrition wheel based therapy, while SPRINT+Glargine included insulin glargine as it showed benefit in reducing nursing workload (N. N.Razak et al., 2016). Meanwhile, STAR protocol (Evans et al., 2012; Stewart et al., 2016) stochastically predicts the next BG from 5% to 95% readings prediction. All of the protocols utilized the current and previous reading of BG, insulin and nutrition to recommend the next treatment of insulin and nutrition based on chosen BG target range. Fig. 1 shows the flowchart for virtual trial simulations that comes in two stages. The first stage, S_I was identified. Meanwhile, in the second stage, each protocol was virtually simulated where the BG control target used was 6.0 – 10 mmol/L, less tight as compared to SPRINT and STAR protocol, but adapting to Malaysian's hospital requirementas shown in Fig. 1.

Model-based protocols performance and safety were evaluated in two cohorts; DM and NDM. The virtual trial results performance was identified through the median and interquartile range (IQR) percentage BG within the time in band (TIB) for three bands which are %BG TIB 4.4 – 8.0 mmol/L, %BG TIB 6.0 – 10.0 mmol/L and %BG>10.0 mmol/L. Patient's median and IQR for BG (mmol/L), the administered insulin (g/hr) and nutrition (g/hr), the number of BG measurements were too identified. The safety assessment was verified by the number of hypoglycaemia episodes for mild hypoglycaemia (BG < 4.0 mmol/L) and severe hypoglycaemia (BG < 2.2 mmol/L).

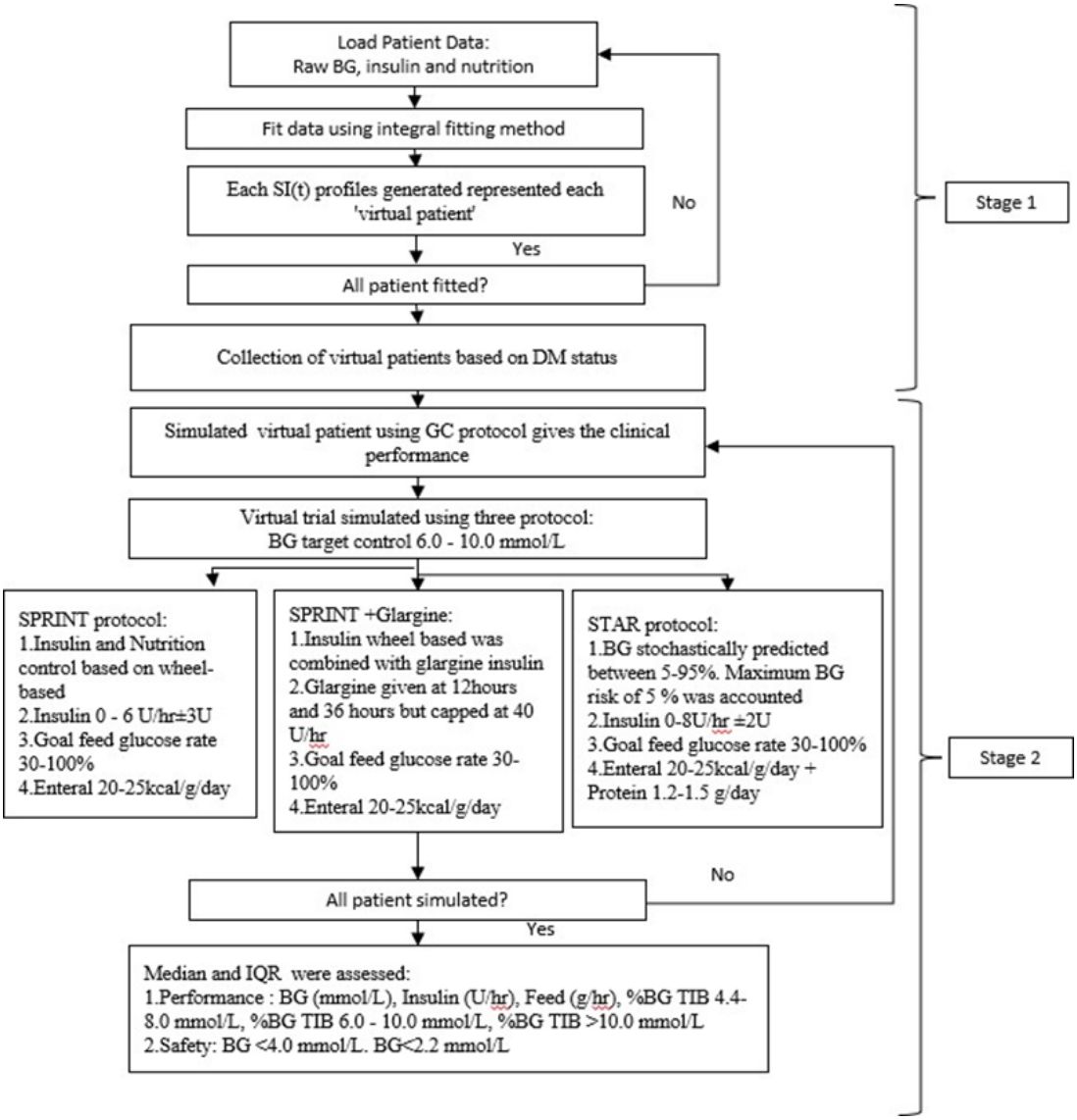

Fig. 1 *Flowchart of virtual trial simulation*

3. Results and Discussion

There are 48.9% out of the 282 patients in the multicentre ICUs have diabetes mellitus. There are 50.7% (70 out of 138) DM female patients and 50.0% (72 out of 144) NDM male ICU patients. The median age is 58 years for both DM and NDM patients. The cohort's age showed no significant difference (p= 0.3268) in all DM and NDM patients from the Mann-Whitney test. However, the median weight for DM and NDM with 69 kilograms and 70 kilograms presented in all patients have a significant difference with a p-value less than 0.05 (p= 0.0138). In addition, there is a significant difference where p-value is <0.05 between for both DM and NDM cohorts in patient's ICU stays.

The difference number in NDM cohorts ethnic compared to DM cohorts are higher in Malay by 22 patients more, but less by 6, 8 and 2 for Chinese, Indian and foreigner patients. The median length of patient stay through theGC treatment indicates an additional difference of 24 hours in NDM patients. As reported in (International Diabetes Federation, 2019), DM patients represent higher percentage with 50.7% for female. From this demographics data in Table 1, the ethnicity statistics were the same as the National Health Morbidity Survey reported in (Ministry of Health Malaysia, 2013) where diabetes patients were higher in Malay followed by Chinese and Indian, compared to (Letchuman et al., 2010).

Fig 2. shows the identified S_I in the patient's profile. The first panel shows the raw BG data (cross) and BG simulated (line). The second panel shows the insulin, I (straight line) and the interstitial insulin, Q (dotted line). Thispatient's S_I in the third panel during the first 5 hours was low and highly varies in between 30 to 50 hours of ICU stays. However, the patient's BG (first panel) is within the desirable range when the patient starts to respond well towards insulin given. The last panel shows the dextrose which is the rate of glucose or nutrition received by the patients and insulin administered (dotted line) during the ICU stays.

Fig. 3 represents an example of a diabetic patient with length of glycaemic control (LGC) more than 120 hours simulated using three model-based protocols which are SPRINT, SPRINT+Glargine and STAR. This patient weight is 93.5 kilograms, with age 64 years old, and was diagnosed with acute kidney infection (AKI) and septic shock. From the first panel, the BG readings show that STAR protocol can reduce and maintain BG at a normoglycaemic level. This shows that the performance % BG of TIB 4.4 - 8.0 mmol/L was the highest with 71.9% for STAR protocol compared to SPRINT and SPRINT+Glargine with 64.4% and 55.6% respectively for this patient. Despite having diabetes mellitus this patient shows no hypoglycaemia episode using STAR virtual trial.

The plasma insulin (I) and interstitial insulin (Q) are shown in the second panel from Fig. 3 were calculated using Equation (2) and (4) for all three protocols. During the first 40 hours of treatment, the patient responded well toinsulin with SPRINT and SPRINT+Glargine protocols which explained the overall reduction of BG level in Fig. 3 together with the results shown in Table 3 for these two protocols. After 40 hours, the results of BG modelled from Equation (1) show that STAR protocol having better control which explained the low BG level and higher hypoglycaemia episode in the other two protocols. The S_I is less dynamics, where the value remains the same but increased after 40 hours of ICU stay when BG level becomes low in all three protocols. In the last panel of Fig. 3, STAR insulin was illustrated in the pink cross line and nutrition in the blue line. Meanwhile, the administered insulin and nutrition for SPRINT and SPRINT+Glargine are represented by the black and green line. Towards the end of the patient's stay, the administered insulin is lower to avoid hypoglycaemia and the amount of nutrition was high.

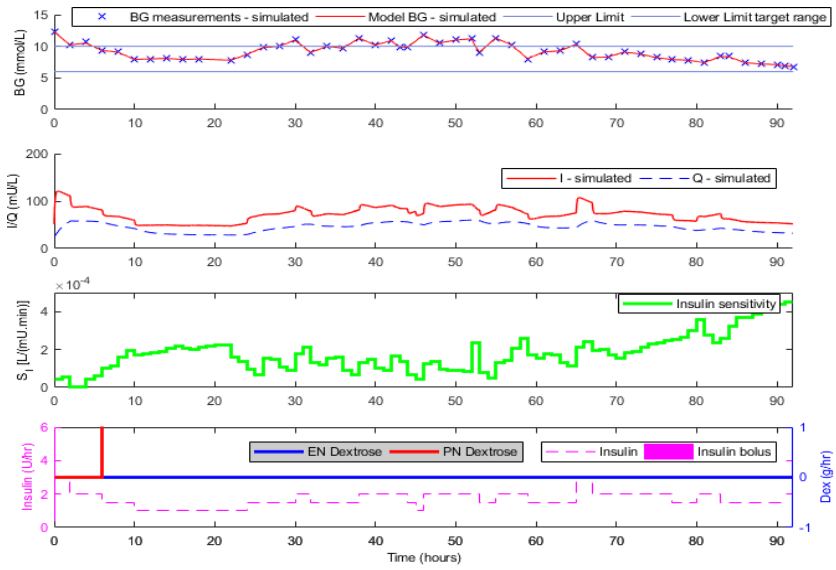

Fig. 2 *Patient's profile with identified insulin sensitivity*

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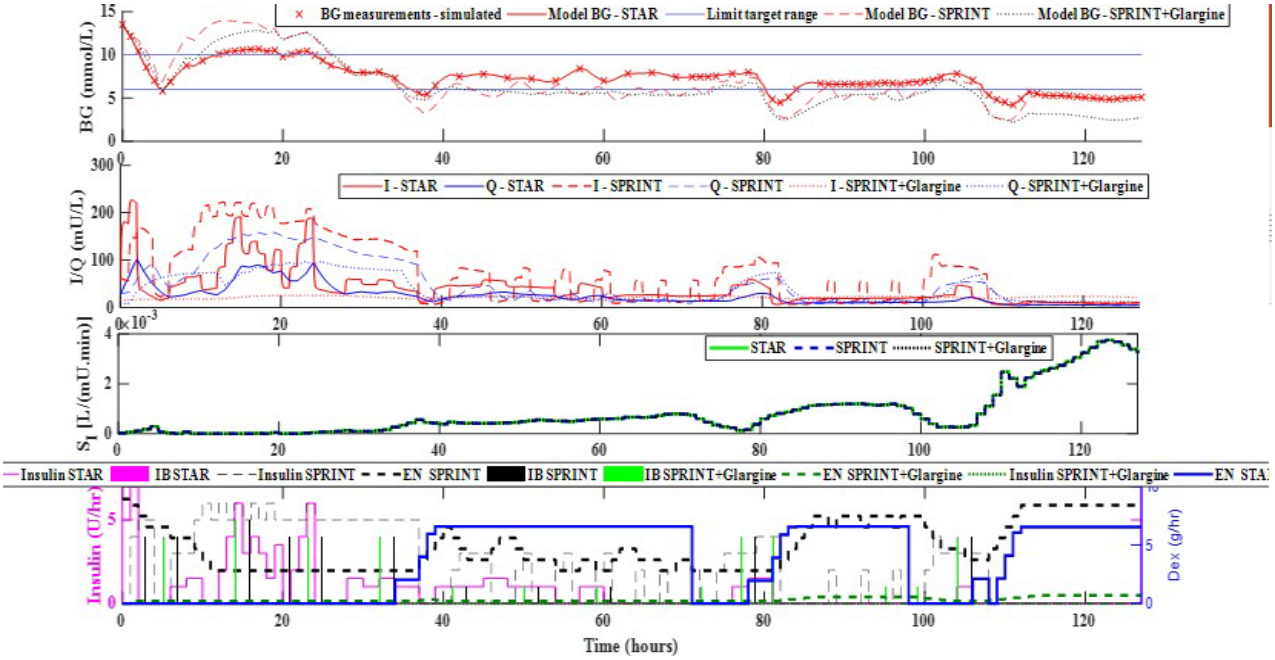

Fig. 3 *Patient's profile for DM patients simulated using SPRINT, SPRINT+Glargine and STAR protocols*

Table 3 shows the virtual trial performances and safety results for clinical, SPRINT, SPRINT+Glargine and STAR protocols in both DM and NDM cohorts. The BG (mmol/L) median and IQR (25^{th} to 75^{th}) for DM patients were lower using SPRINT+Glargine and SPRINT control with 7.40 [5.63 – 10.86] mmol/L and 7.42 [5.92 – 10.84] mmol/L. The STAR and clinical protocol's BG reading median and IQR are 8.91 [7.12 – 10.58] mmol/L and 9.40 [7.60 – 11.50] mmol/L. Although the BG median in SPRINT and SPRINT+Glargine is lower compared to STAR control, the %BG TIB shows higher improvement for performance control target 6.0 – 10.0 mmol/L. The insulin andnutrition median and IQR given in STAR protocol is somewhat consistent to clinical protocol based on this in-silico analysis. Meanwhile, SPRINT and SPRINT+Glargine protocols gave lower nutrition value with a difference of 2.1 g/hr and 4 g/hr in median than clinical protocol in the both DM and NDM cohorts.

The administered insulin median and IQR for STAR versus SPRINT are 2.0 [0.0 – 4.0] vs. 4.0 [2.0 – 5.0] in DM and 1.5 [0.0 – 3.0] vs. 3.0 [0.0 – 5.0] U/hr in NDM patients. The virtual simulation results in SPRINT and SPRINT+Glargine protocols demonstrated to administer higher insulin compared to the clinical protocol. This may resulted in low BG reading but leads to higher incidence of severe hypoglycaemia. However, STAR administered insulin and nutrition given were similar to clinical showing that STAR can still control BG level while having consistent median and IQR insulin and nutrition value as clinical. Moreover, the % BG TIB 6.0 – 10.0 mmol/L performance showed that with STAR protocol, the BG within the target range improved significantly in DM and NDM with percentage increased by 16.7% [19.1 – 14.8] and 11.7% [10.9 – 13.6]. Since Malaysian BG control was set to 6.0 – 10.0 mmol/L, the median % BG TIB for STAR shown is 71.6% and 77.6% in DM and NDM while for STAR Christchurch and STAR Hungary was 82.6% and 85.7% (Stewart et al., 2016), respectively. These differences in median performance compared to the another two countries for DM and NDM was 11% and 14.1%. The difference in percentage showed that DM and NDM patients possibly have higher BG variability as the response towards insulin needs time.

The number of BG measurements of STAR vs. clinical in Table 3 shows an increasing number of 3826 and 5591 counts for DM and NDM patients. As STAR suggests frequent measurement between 1 to 3 hours to reduce hyperglycaemia higher than 10.0 mmol/L, this is reflected in the numbers of BG measurements. However, amongst these three protocols, STAR showed the lowest interventions for glycaemic control compared to SPRINT and SPRINT+Glargine. Although the frequency of BG measurements is lower in clinical ICU settings, the median and IQR BG reading showed that through this virtual trial simulation STAR provides consistent results to the clinical protocol but with better performance outcome. Besides, the multicentre's BG measurements in clinical used to take measurement between 1 to 4 hours which showed the real frequency measurements have less strict protocols. From Table 2, the results demonstrated that STAR is efficient in performance that ensure patient's safety when delivered the personalized care with low number of severe hypoglycaemia.

Although mainly, the workload for STAR can still be considered high compared to (Stewart et al., 2016) STAR still provides better patient's outcome with the lowest number of hypoglycaemia compared to other two

protocols. It is worth noting, that ICU DM patients are sensitive to the critical care setting surrounding and highly dynamic dueto stress and high resistance towards insulin response. In future, STAR controller intervals could be increased from 1to 3 hours to 4 to 6 hours to identify how these patients respond with less interventions. Since the type of insulin used was infusion, another option that can be simulated is through a combination of basal bolus insulin such as glargine to reduce clinical intervention.

Table 3 *Virtual trial performance and safety results for all ICU patients. Median and interquartile range is illustrated as needed*

Parameter	Clinical		SPRINT		SPRINT+Glargine		STAR	
	DM	NDM	DM	NDM	DM	NDM	DM	NDM
BG (mmol/L)	9.40 [7.60 - 11.50]	8.60 [7.10 - 10.50]	7.42 [5.92 - 10.84]	6.52 [5.60 - 8.96]	7.40 [5.63 - 10.86]	6.37 [5.38 - 9.42]	8.91 [7.12 - 10.58]	7.85 [6.52 - 9.74]
Insulin (U/hr)	2.0 [1.0 - 3.0]	1.0 [0.0 - 2.0]	4.0 [2.0 - 5.0]	3.0 [0.0 -5.0]	4.0 [1.0 - 4.0]	3.0 [0.0 - 4.0]	2.0 [0.0 - 4.0]	1.5 [0.0 - 3.0]
Nutrition (g/hr)	4.1 [0.0 - 6.1]	4.1 [0.0 - 6.7]	2.0 [2.0 - 2.6]	2.0 [2.0 - 3.3]	0.1 [0.1 - 0.1]	0.1 [0.1 - 0.1]	3.9 [0.0 - 6.6]	4.1 [0.0 - 6.6]
%TIB BG 4.4 - 8.0 mmol/L	25.9 [15.0 - 41.0]	32.1 [20.5 - 55.4]	52.4 [26.0 - 71.4]	69.1 [46.5 - 84.3]	53.0 [32.0 - 70.7]	62.1 [40.9 - 79.7]	38.8 [19.8 - 60.0]	51.2 [38.3 - 67.6]
%TIB BG 6.0 - 10.0 mmol/L	54.9 [38.2 - 65.0]	65.7 [52.0 - 75.2]	45.6 [33.3 - 55.1]	53.8 [44.6 - 64.3]	49.6 [35.6 - 61.3]	46.7 [33.4 - 62.2]	71.6 [57.9 - 79.8]	77.4 [62.9- 88.8]
%BG>10.0 mmol/L	38.4 [24.4 - 55.2]	27.5 [13.7 - 43.4]	27.6 [11.8 - 48.6]	10.9 [3.5 - 27.1]	21.0 [9.6 - 39.9]	10.8 [7.3 - 26.6]	22.7 [9.2 - 37.9]	10.4 [3.6 - 26.7]
Nb. BG<4.0 mmol/L	31	32	71	85	71	74	29	33
Nb. BG<2.2 mmol/L	4	6	7	15	10	21	3	7
Nb. BG measurement	6990	7388	11367	14132	11928	13575	10816	12878

4. Conclusion

Glycaemic control can be more effective, productive, safe, and cost-saving with model-based glycaemic control through in-silico trial validations in monitoring patient's outcomes. Virtual trials using three protocols were validated based on the performance and safety metrics using personalized care in this study. ICING model that was governed by STAR protocol has demonstrated the highest percentage TIB in BG 6.0 – 10.0 mmol/L performance amongst other clinical protocol performance with lower number of hypoglycaemia cases which closely resembles clinical results. This means STAR protocol provides better performance and safety for glycaemic control. Although, the clinical BG level in DM patients are more dynamics from the identified S_I which may highly impacting the BG variability and performance in those cohorts. STAR protocol can provide similar situation to the clinical data but with higher performance through this virtual trial analysis. A transition of sliding-scale insulin therapy to a personalized model-based glycaemic control can be achieved, despite having some challenges in regards to insulin intervention or workload trust from clinician may play a huge role on adapting STAR protocol.

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Conflict of Interest

Authors declare that there is no conflict of interests regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and design, analysis, interpretation of results****: AAR;* ***draft manuscript preparation****: AAR, NNR, NNHS, AAS;* ***data collection****: AAR, UJ, FS. All authors reviewed the results and approved the final version of the manuscript.*

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