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Performance of Stochastic Targeted Blood Glucose Control Protocol by virtual trials in the Malaysian intensive care unit

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ABSTRACT

Background and objective: Blood glucose variability is common in healthcare and it is not related or influenced by diabetes mellitus. To minimise the risk of high blood glucose in critically ill patients, Stochastic Targeted Blood Glucose Control Protocol is used in intensive care unit at hospitals worldwide. Thus, this study focuses on the performance of stochastic modelling protocol in comparison to the current blood glucose management protocols in the Malaysian intensive care unit. Also, this study is to assess the effectiveness of Stochastic Targeted Blood Glucose Control Protocol when it is applied to a cohort of diabetic patients.

Methods: Retrospective data from 210 patients were obtained from a general hospital in Malaysia from May 2014 until June 2015, where 123 patients were having comorbid diabetes mellitus. The comparison of blood glucose control protocol performance between both protocol simulations was conducted through blood glucose fitted with physiological modelling on top of virtual trial simulations, mean calculation of simulation error and several graphical comparisons using stochastic modelling.

Results: Stochastic Targeted Blood Glucose Control Protocol reduces hyperglycaemia by 16% in diabetic and 9% in nondiabetic cohorts. The protocol helps to control blood glucose level in the targeted range of 4.0–10.0 mmol/L for 71.8% in diabetic and 82.7% in nondiabetic cohorts, besides minimising the treatment hour up to 71 h for 123 diabetic patients and 39 h for 87 nondiabetic patients.

Conclusion: It is concluded that Stochastic Targeted Blood Glucose Control Protocol is good in reducing hyperglycaemia as compared to the current blood glucose management protocol in the Malaysian intensive care unit. Hence, the current Malaysian intensive care unit protocols need to be modified to enhance their performance, especially in the integration of insulin and nutrition intervention in decreasing the hyperglycaemia incidences. Improvement in Stochastic Targeted Blood Glucose Control Protocol in terms of u_{en} model is also a must to adapt with the diabetic cohort.

1. Introduction

Recently, the number of people suffering from chronic diseases such as heart complication and diabetes has increased significantly [1]. If these life-threatening diseases are not cured, it results in mortality in critical care [2,3]. Patients admitted in intensive care unit (ICU) usually experience stress-induced hyperglycaemia (high blood glucose level) [4], especially for those with diabetic history. Diabetic patients have higher mean of blood glucose (BG) and higher risk of having hypoglycaemia (low BG level) than patients without diabetes [5]. Blood glucose issues occur in two situations, either hyperglycaemia or hypoglycaemia. Hypoglycaemia and extreme hyperglycaemia should be avoided since they are correlated with mortality and critical patients in the ICU have higher risk of developing complication [6].

Maintaining a safe and effective control of BG is difficult because the response for each critically ill patient is complex, variable and dynamic [7]. Therefore, the application of intensive BG management or protocol in ICU is important in controlling the BG level and preventing BG issues (hyperglycaemia and hypoglycaemia) [8]. BG protocol is developing, where it has transformed

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from manual (paper-based) to computerised (tablet based) system. However, previous studies have shown failure in achieving consistent, safe and effective BG control [9–12].

The application of a computerised model-based BG control protocol in ICU is carried out since 2011 [13–16]. Known as stochastic targeted (STAR), this protocol can identify patient-specific parameters and customise clinical treatment based on patient metabolic state. STAR, a tablet- based protocol is an advanced version of Specialised Relative Insulin and Nutrition Tables (SPRINT) [12].

The SPRINT protocol manages to reduce organ failure and mortality [12,17]. SPRINT is insulin administration via patient-specific approach, where it accounts for inter- and interpatient variability, which provides the tightest control among the patients [18,19]. However, the protocol is inflexible, and the clinical burden is higher than desired [13].

To compensate the clinical burden, STAR is currently implemented in ICUs. STAR is a clinically validated physiological model of the glucose-insulin system [20] and it is based on population model of insulin sensitivity (SI) variability [21]. Besides, it is able to conduct optimal patient-specific insulin and nutrition treatment that maximise control and nutrition, where it also maintains hypoglycaemia incidence at a maximum of 5% risk [22]. Since 2011, STAR is recognised as a standard practice of care in the Christchurch Hospital ICU, Christchurch, New Zealand, and in the Kalman Pandy Hospital ICU, Gyula, Hungary. The study of STAR development and protocol comparison shows that STAR protocol reduces 79% hypoglycaemia than the SPRINT protocol [16].

Apart from STAR and SPRINT, insulin infusion therapy (IIT) that applies therapeutic approach is another BG control protocol. It reduces morbidity and increases survival rate in some critical care patients, however it is associated with a risk of hypoglycaemia if high insulin dose is administered to the patients [23–25]. A few strategies such as having wider BG target range, sliding scale insulin titration, increased frequency of BG concentration measurement, and higher caloric intake are used to minimise the risk of iatrogenic-induced hypoglycaemia during IIT [26–28]. IIT practice fully depends on insulin infusion, which places nutrition or carbohydrate to the protocol of its own. Studies done on IIT discovered that only 79% patients tested who were tested separately are in the targeted range and they were having problem to control hypoglycaemia, where 37 patients who underwent IIT had hypoglycaemia. This shows that BG control is difficult using IIT [16,29]. Thus, IIT needs to be revised to encounter its weakness.

Currently, the Malaysian ICU protocol in BG level control is implementing IIT, which is adjusted to adapt with the clinical environment and behaviour of local cohort. The Malaysian government has published BG protocol guidelines in ICU [30], but when it comes to the practice in hospital setting, the protocol is altered according to the patient needs. This happens because the existing BG controller does not fully work and improvements are still ongoing. Often, IIT is poorly controlled, this leads to BG variability thus increases the length of stay (LOS) in ICU. STAR can reduce mortality as it shortens the LOS for a patient to 3 days at most, as compared to IIT which is up to 6 days [31,32]. Another issue of concern in ICU is hypoglycaemia which the weaknesses of the current BG protocol need to be resolved.

Overall, BG control protocols are important to reduce the risk of mortality by maintaining BG at normal level, this determines the efficacy and safety in ICU [9,11,15,33]. This study is focused on the performance and the comparison between computerised STAR BG control and the Malaysian ICU protocol, pertaining to the patient BG level and insulin sensitivity (SI). In fact, this control mechanism targets the BG level output of 4.0–10.0 mmol/L. Also, comparison of variables (BG level and SI) between diabetes and non-diabetes critically ill patients will be computed to see the reliability of STAR protocol in controlling BG level under diabetes circumstances.

Table 1
Summary of patient socio-demographics.

	Diabetic	Non Diabetic
Number of patients	123	87
Female/Male	58/65	33/54
Age (years)	58[50–65]	53.9[36–62]
BMI (kg/m^2)		
<18.5 (underweight)	2	1
18.5–24.9 (normal range)	41	42
≥25 (overweight)	80	44
Ethnicity		
Malay	104	72
Chinese	9	6
Indian	5	2
Original people	–	2
Others	5	5
ICU category		
Medical	83	48
ENT	3	1
Surgical	29	30
Neurology	6	8
Ophthalmology	1	–
Urological	1	–

2. Methods

2.1. Clinical data

From the Malaysian ICU protocol, BG level, nutrition and insulin infusion inputs of 210 critically ill patients treated at the Intensive Care Unit (ICU) in Hospital Tengku Ampuan Afzan (HTAA), Kuantan [30] were collected from May 2014 until June 2015. There were 123 patients out of 210 are having comorbid diabetes (mostly Type 2 Diabetes) besides having other primary illnesses such as acute kidney injury and sepsis. The patient medical records were extracted from case report form (CRF). Table 1 summarises patient sociodemographic characteristics where virtual patients are created from this clinical data. It also represents HTAA cohort, which will be compared with the results from the STAR protocol.

2.2. ICING physiological model

The study obtained ethics approval from the National Institutes of Health (NIH) NMRR-13-1592-18,706 (HTAA) and the Research Management Centre (IIUM)-IREC657 (IIUM MC). In some cases, physiological parameters cannot be measured directly and the measurement of certain parameters within the required frequency is inefficient [21]. Therefore, model-based method is applicable to specify the physiological parameters [21]. The clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model is developed for critical-ill patients [20,34], which is used to identify SI for each patient. SI was monitored hourly using iterative integral-based method [35] and it represents the “whole-body” SI [21].

Via the ICING model, the relation between glucose decay rate and insulin concentration in the interstitium is scrutinised to assess SI. SI is defined as the insulin response (via pancreas) to the increase of BG level, where cells absorb BG when being stimulated by insulin. This parameter is used to guide model-based, tight blood glucose control in several studies [32,36,37]. The model equations are defined as;

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

$$\dot{Q}(t) = n_I(I(t) - Q(t)) - n_C\frac{Q(t)}{1+\alpha_G Q(t)} \quad (2)$$

$$\dot{I}(t) = n_K I(t) - n_L \frac{Q(t)}{1+\alpha_G Q(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_1} + (1 - x_L)\frac{u_{en}(G)}{V_1} \quad (3)$$

$$\dot{P}_1\ (t) = -d_1 P_1 + D(t) \quad (4)$$

$$\dot{P}_2\ (t) = -\min\left(d_2 P_2, P_{\max}\right) + d_1 P_1 \quad (5)$$

$$P(t) = \min(d_2 P_2, P_{\max}) + PN(t) \quad (6)$$

$$u_{en}(G) = \min(\max(16.67, k_1 G(t) + k_2), 266.67) \quad (7)$$

where $G(t)$ [mmol/L] is the total plasma glucose, $I(t)$ [mU/L] is the plasma insulin, and the interstitial insulin is represented by $Q(t)$ [mU/L]. The exogenous insulin input is represented by $u_{ex}(t)$ [mU/min] and the endogenous insulin secretion is estimated with $u_{en}(G)$ [mU/min], which is modelled as a function of plasma glucose level of critically ill patients with a minimum pancreatic output of 1 U/h up to maximum of 16 U/h [38]. In addition, k_1 is the pancreatic insulin secretion glucose sensitivity and k_2 is the pancreatic insulin secretion offset. The first-pass insulin clearance at liver is represented by x_L, and n_I [1/min] accounts for the transfer rate between plasma and interstitial insulin compartments. The patient endogenous glucose clearance and insulin sensitivity are p_G [1/min] and SI [L/mU.min]. Meanwhile, V_I [L] is the insulin distribution volume, n_K [1/min] and n_L [1/min] represent the insulin clearance from plasma via kidney and liver, respectively. Basal endogenous glucose production (unsuppressed by glucose and insulin levels) is denoted by EGP [mmol/min] and V_G [L] represents glucose distribution volume. CNS [mmol/min] represents noninsulin-mediated glucose uptake via the central nervous system. The Michaelis-Menten kinetics are used to model saturation, with α_I [L/mU] for the saturation of plasma insulin clearance via liver, α_G [L/mU] for the saturation of insulin-dependent glucose clearance and receptor-bound insulin clearance from interstitium. P_1 [mmol] and P_2 [mmol] represent glucose concentration in the stomach and gut respectively. The transfer rate between the stomach and gut is represented by d_1 [1/min], and the transfer rate from gut to bloodstream is d_2 [1/min]. The enteral glucose input is denoted by $P(t)$ [mmol/min], and P_{max} represents the maximum disposal rate from the gut. All constant parameter values can be referred from the previous study by Lin et al. [20].

2.3. Malaysian ICU protocol

Currently, Hospital Tengku Ampuan Afzan (HTAA) in Kuantan implements two ICU protocols in controlling insulin and nutrition, namely the Insulin Infusion Therapy and the Enteral and Parenteral Nutrition Protocol (known as the Malaysian ICU protocol) [30].

2.3.1. Insulin infusion therapy

This protocol is conducted by recording two BG readings consecutively within 1 h, when BG is greater than 10.0 mmol/L. Soluble insulin 50 units in 50 mL 0.9% NaCl is used as continuous intravenous insulin infusion. The targeted BG range is between 4.0–10.0 mmol/L for Malaysian cohort. At the beginning, BG level is monitored hourly, until it reaches the targeted range. Then the next measurement is done within 2 h, if the insulin rate of change is not required within the timeframe. The frequency of BG level monitoring can be reduced to 4 h once BG level is within the targeted range.

Table 2
Insulin infusion rate.

BG level [mmol/L]	Infusion rate [U/h]
8.1 – 11.0	2
11.1 – 15.0	3
>15.0	4

The initial insulin infusion rate of Insulin Infusion Protocol is presented in Table 2. When insulin is administered to patients, 10% dextrose infusion is initiated, maintained at 25 mL/h until the Enteral Nutrition (EN) has stabilised (i.e. 40 mL/h with 200 mL aspirate) or once the Total Parenteral Nutrition (TPN) has started. Then, BG level is monitored hourly while the insulin infusion rate is adjusted (sliding scale method) for 2 consecutive hours at a constant rate. If BG level is in the targeted range, it can be measured within 2 to 4 h. If there is adjustment in the insulin infusion rate or changes in dextrose/EN/TPN, BG level has to be monitored hourly.

2.3.2. Enteral and parenteral nutrition protocol

Enteral feeding is preferable in critical care unit as compared to the parenteral nutrition. Therefore in this study, parenteral nutrition is dismissed.

Enteral nutrition depends on aspirate reading, which is a measurement of gastric content or fluid withdrawn from the body. Often, enteral feeding starts after 24–48 h of admittance in Intensive Care Unit (ICU), which is summarised as:

a. Feeding is initiated 20–40 mls/h within 4 h via aspirate feeding tube.
b. After 4 h:
i. If aspirate is lesser than 200 mls/h, return the aspirate and increase the rate by 20 mls/h for 3 cycles, until it meets the patient caloric needs.
ii. If aspirate is higher than 200 mls/h, return the aspirate to patient and reduce it by 50% of the initial rate.

2.4. Virtual trial simulations

Prior to the clinical implementation, virtual trial enables new BG control protocols to be tested [13]. Virtual trial is a pilot test, where the clinical data undergo a new BG control protocol to compute a new processed data known as virtual patient. Its main purpose is to validate and prove the protocol feasibility with the cohort environment. The clinical and virtual data analyses are compared to identify the best protocol in treating the diseases. These trials are to optimise BG control, safe from hypoglycaemia risk, clinical burden, and it can handle dynamic change in patient metabolic state or unanticipated effect prior to clinical implementation [39–41].

Fig. 1 shows the simulation of virtual patients based on clinical data obtained from ICU in HTAA. Clinical data are used to identify patient-specific SI profile via the ICING model, by applying the iterative integral-based method [35]. Based on the SI profile and baseline measurement of BG level, nutrition and insulin inputs, STAR virtual trial is simulated to generate BG response of the virtual patients hourly.

Then, SI of the virtual patients who undergo the Malaysian ICU protocol is resimulated using ICING model and STAR controller. The trial simulation outcomes are based on per-cohort and per-patient statistics of insulin rate, dextrose rate and percentage of hourly BG. The STAR controller uses patient-specific SI to project the next patient treatment.

In the virtual trial simulation, STAR protocol is used to monitor patient BG and nutrition inputs. The STAR protocol is for those patients with BG level higher than 10.0 mmol/L in 2 consecutive

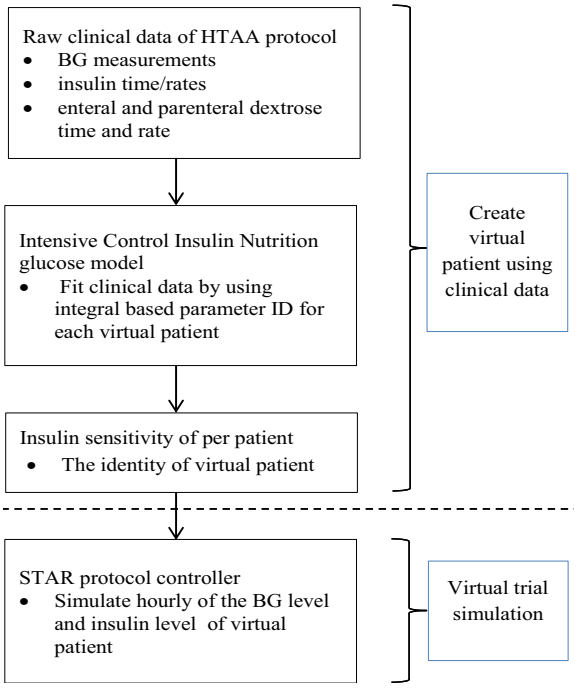

Fig. 1. Development of virtual patient and STAR virtual trial simulation.

hours [12]. For this protocol, nurses are free to select the next BG measurement, either within interval of 1 h, 2 h, or 3 h once BG level is in the targeted range.

2.5. Analysis

The BG percentage within the targeted range of 4.0–10.0 mmol/L represents the protocol performance. The performance of the STAR protocol was compared with the Malaysian ICU protocol, by looking at the median and interquartile values of the BG, between the current protocol and STAR protocol.

Since BG and insulin reading is skewed, nonparametric statistics are used for all comparative tests in this study. In addition, the Kolmogorov-Smirnov test is used to calculate the p-value of the continuous data. An ANCOVA test is used to prove the existence of covariate(s). Results of all tests are statistically significant if the p-value are below 0.05.

2.6. Study limitations

The data were only collected from one Malaysian government hospital (HTAA). In general, all ICUs in the Malaysian general hospitals follow the guidelines provided by the Ministry of Health Malaysia, as described in Sections 2.3.1 and 2.3.2 [30,42,43]. Hence, the results obtained are generalised for all ICUs in the Malaysian general hospitals. In certain circumstances, the physicians dismiss the protocol because of some factors (e.g. different diagnostic, patient needs). However, the implementation of a standard protocol is compulsory for all general hospitals in Malaysia.

3. Results

Table 3 depicts the results of 210 patients who underwent the Malaysian ICU and STAR virtual protocols. They are classified into diabetic and nondiabetic groups. Table 3 indicates the simulation results via virtual trials based on BG level, glucose and insulin rate, and number of patients. In general, the statistical output shows that the virtual STAR performance is better than the Malaysian ICU protocol, for both diabetic and nondiabetic patients because the median, mean, and standard deviation of BG level of the former are lower.

The targeted range of BG level is 4.0–10.0 mmol/L, which is reflected in percentage, as shown in Table 3. STAR values for both diabetic and nondiabetic patients were 71.8% and 82.7%, respectively, which are higher than the results obtained from the Malaysian ICU protocol. Insulin and glucose rates are dependent to each other. Both rates interact with the ratio of 1:1. However, there are some issues that affect the reading of median insulin and glucose rates in Table 3 (to be explained in the discussion section).

The resampled means of BG in Table 3 were interpolated to obtain only one BG value per hour. If data were not resampled, the comparison is invalid because STAR allows less frequent measurement once the patient reaches the targeted range and this requires measurement in one-hour interval once the BG level is outside the range. Thus, BG measurement tends to be biased towards the poor ones.

Fig. 3 shows the SI stochastic model of the STAR virtual trial. SI has higher variability (wider range), where the huge decline of SI in the 5th percentile is common and more prevalent. The BG levels fitted with diabetes and nondiabetic patients based on the ICING physiological model and STAR virtual trial are illustrated in Fig. 2 (b and d). It shows that patients with diabetes have erratic BG response, which is often outside the targeted range while BG fitted with the ICING model in nondiabetic cohort are shown in Figure (a and c) as well. The boxplot in Fig. 4 compares the current Malaysian ICU protocol and STAR virtual trials. The BG measurement error of the data fitted with the ICING physiological model is depicted.

4. Discussion

In general, BG control protocols implemented in ICU worldwide are designed without looking at the specific group - diabetes patients. Table 3 shows that 59% of the sample are diagnosed with type 2 diabetes mellitus. It is shown that STAR works for both cohorts, with improvement of median BG in diabetic (7.6 mmol/L) and nondiabetic (7.1 mmol/L) patients. The median BG is within the targeted range of 4.0–10.0 mmol/L when nutrition and insulin are sufficiently provided. So, higher insulin input is required for diabetic cohort, in which the glucose to insulin ratio is reasonable, where STAR recorded 4.5 U/hr (insulin) with 3.6 g/hr (glucose) for diabetic cohort and 4.0 U/hr (insulin) with 4.5 g/hr (glucose) for nondiabetic cohort. In fact, the glucose-insulin monitoring system (STAR in comparison to conventional protocol) reduces hyperglycaemia incidence (BG > 10 mmol/L) almost by 16% in diabetic patients and 9% in nondiabetic patients. Thus, the patients that reached the targeted BG level increased to 71.8% (diabetic cohort) and 82.7% (nondiabetic cohort). This proves that STAR can be implemented in the Malaysian ICU as it reduces the hyperglycaemia and increases the BG level within the targeted range (4.0–10.0 mmol/L).

On the other hand, Table 3 shows that the current Malaysian ICU protocol is ineffective in controlling BG, where the medians are 9.1 mmol/L and 8.0 mmol/L in diabetic and nondiabetic cohorts, respectively. The median BG in diabetic cohort is high since the value is close to the upper limit of the targeted range (10.0 mmol/L). So far, the BG control protocols implemented in the Malaysian ICU consider both insulin and nutrition levels, which are done separately. This may cause insufficient insulin administration with respect to the glucose intake of critically ill patients based in the conventional IIT protocol. Simulation results show that with low dose of insulin (2.0 U/hr) administered to the both cohorts (diabetic and nondiabetic), the risk of hyperglycaemia increases by 15% in diabetic cohort as compared to the nondiabetic cohort. Mean-

Table 3
Summary of two subgroups based on diabetic and non-diabetic from Malaysian ICU Protocol and STAR Protocol.

Whole cohort statistics	Malaysian ICU diabetic	STAR diabetic	Malaysian ICU non-diabetic	STAR non-diabetic
Number of patients:	**123**	**123**	**87**	**87**
Total hours	**15,779**	**15,708**	**10,948**	**10,909**
BG median (mmol/L)	**9.1 [7.1–11.4]**	**7.6 [5.7–9.8]**	**8.0 [6.6–9.9]**	**7.1 [5.7–8.9]**
BG mean (mmol/L)	**9.0**	**7.4**	**8.1**	**7.1**
BG StDev (mmol/L)	**1.4**	**1.5**	**1.4**	**1.4**
% BG 4.0–10.0 mmol/L	**59.0**	**71.8**	**75.2**	**82.7**
% BG > 10.0 mmol/L	39.0	22.9	23.6	14.5
% BG < 4.0 mmol/L	1.9	5.3	1.2	2.8
Num patients < 2.2 mmol/L	7	29	2	7
Median insulin (U/hr)	2.0 [1.0–3.0]	4.5 [2.0–8.0]	2.0 [1.0–3.0]	4.0 [2.0–7.5]
Median glucose (g/hour)	2.6 [2.6–5.7]	3.6 [1.9–5.8]	5.7 [2.6–6.1]	4.5 [1.9–6.6]
Hourly resampled stats:				
% BG 4.0–10.0 mmol/L	**61.4**	**80.4**	**77.1**	**89.6**
% BG > 10.0 mmol/L	37.5	15.8	22.3	8.6
% BG < 4.0 mmol/L	1.2	3.8	0.6	1.8
Num patients < 2.2 mmol/L	7	29	2	7

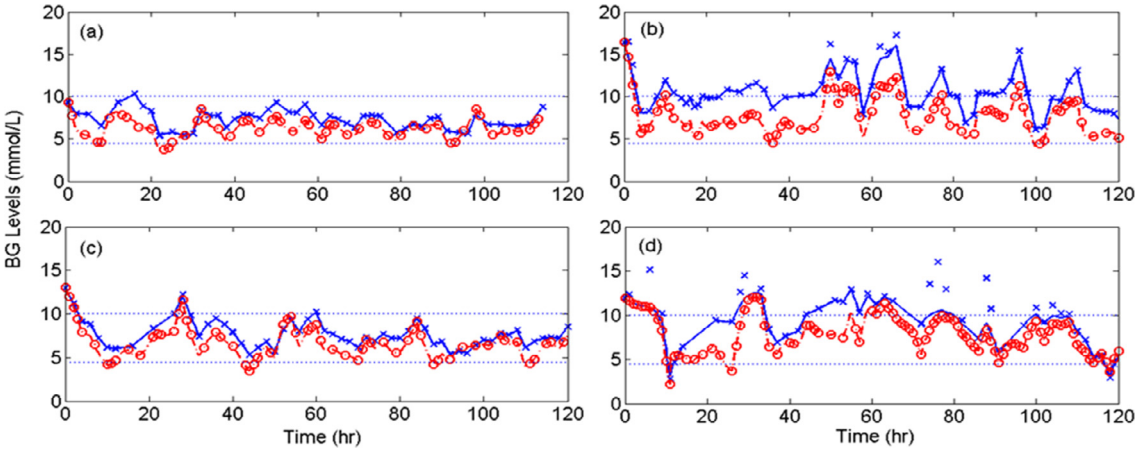

Fig. 2. Examples of *good* BG fitting for (a) non-diabetes and (b) diabetes patients and *poor* BG fitting for (c) non-diabetes and (d) diabetes patients based on ICING physiological model and STAR virtual trial. Note: *cross marks* are the raw BG level clinical data while *circle marks* are STAR virtual trial simulation data. Also, *solid line* indicates the BG level fitting using raw data and ICING model while *dash line* indicates prediction of BG level STAR simulation fitting based on ICING model and *SI* obtained from stochastic model. The *dotted* lines indicate the targeted band of 4.4 – 10 mmol/L.

while, the patients with targeted BG range in the Malaysian ICU are also lower than the STAR virtual trial, by 13% in diabetic and 8% in nondiabetic cohorts.

STAR protocol is designed to control insulin and nutrition simultaneously while balancing BG level in patients, which is determined from SI parameter. When patients have low BG level, high nutrition intake is suggested via the protocol and vice versa. The insulin-nutrition mechanism is developed via a model illustrated in STAR protocol [13,16]. In addition, STAR does not only provide BG and insulin levels, it also predicts BG level for the next hour and suggests the best treatment for a patient accordingly, thus reducing clinician burden, where the total treatment hour can be cut down to 71 h for diabetic cohort and 39 h for nondiabetic cohort, as shown in Table 3.

The results are supported from the previous studies, where STAR helps to reduce the nursing workload up to 60 min for each patient in a day [31]. This shows that STAR is practical to be implemented in the Malaysian ICU to reduce the clinical burden, since diabetes is one of the diseases that requires strict clinical monitoring when being treated with the conventional sliding scale method in critically ill patients.

The current practice of Malaysian ICU protocol was designed based on the study on the sliding scale method. The current Malaysian ICU BG control protocol consists of two protocols, namely IIT and Enteral and Parenteral Nutrition [30]. Different from STAR, both are conducted separately, and both are paper-based models. When the implementation of this protocol fails to solve the complications, clinical judgement by the physicians is required.

Meanwhile, the Enteral and Parenteral Nutrition protocol solely depends on the aspirate level. Aspirate is the liquid materials found in airway or respiratory tract such as gastric contents, saliva, food, or nasopharyngeal. However, this standard practice requires feedings with residual volume of more than 150–200 mL, this puts patients at a risk of gastroesophageal reflux and potential aspiration [44]. There is no evidence to show that the amount of gastric residual volume is safe for them [45]. Therefore, the current nutrition protocol needs to be revised, instead of only depending on the gastric residual volume (aspirate level), it needs to consider insulin input administered to patients based on comorbidity. This is to reduce inadequate nutritional support faced by patients because feedings are held with a predetermined, institution-specific gastric residual volume [44].

In fact, patients with type 1 diabetes mellitus (T1DM) cannot depend on endogenous insulin secretion as their pancreas are unable to secrete sufficient insulin to reach the normal BG level [46]. Thus, patients need external insulin either via infusion or bolus (e.g. insulin pump). BG response in the diabetic cohort is unpredictable and sometimes gets outside the targeted range. The behaviour for both cohorts (diabetic and nondiabetic) is plotted in

Table 4
ANCOVA table of diabetic mellitus covariates with comorbidities.

Source	Type III sum of squares	df	Mean square	F	Sig.
Corrected model	5.5E-8[a]	3	1.8E-8	10.9	<0.05
Intercept	4.2E-9	1	4.2E-9	2.5	
DM	8.1E-9	1	8.1E-9	4.8	<0.05
CM	4.5E-9	1	4.5E-9	2.7	
DM * CM	1.0E-8	1	1.0E-8	6.0	<0.05
Error	3.5E-7	206	1.7E-9		
Total	4.5E-7	210			
Corrected total	4.0E-7	209			

DM – Diabetic Mellitus.
CM – Comorbidities.

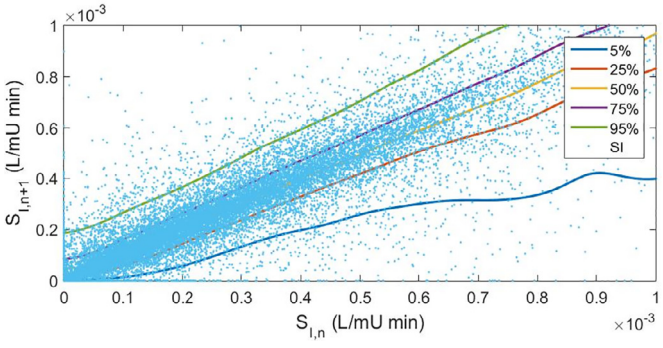

Fig. 3. Stochastic modelling of SI based on overall 210 Malaysian ICU retrospective data underwent STAR virtual trial simulations.

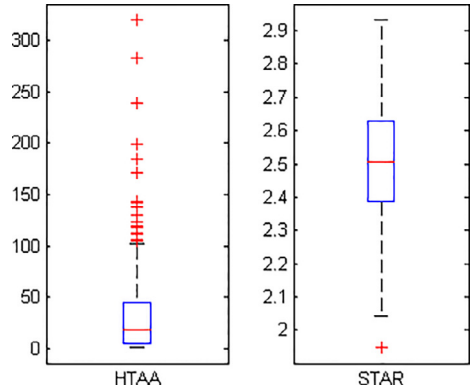

Fig. 4. Boxplot of Malaysian ICU and STAR BG measurement error compared to BG virtual trial simulations and clinical data. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 2, which illustrates that STAR is better in controlling BG level to be within targeted range than the Malaysian ICU protocol. The unfitted data points in Fig. 2 may due to the insufficient nutrition/insulin administered to the patients when they underwent BG control protocol in the ICU.

However, BG response shown in Fig. 2 (a and c) for nondiabetic cohort is fitted with the ICING model. This proves that the ICING model is good in representing the glucose-insulin kinetics of the critically ill patients. However, adjustment and improvement of the u_{en} for diabetic cohort should be validated based on the Malaysian ICU data to improve the feasibility of STAR protocol before being implemented in Malaysian ICU.

By referring to the Eq. (7) of the ICING model, u_{en} illustrates the endogenous insulin secretion of critically ill patients, which affects SI in Eq. (1). Based on Fig. 3, low SI values in the 5th percentile is due to the diabetic patients and multiple comorbidities experienced by the critically ill patients, such as acute kidney injury (AKI), cardiovascular or sepsis besides having diabetes [44]. An ANCOVA analysis was performed and tabulated in Table 4, thus proves that covariation between comorbidity and diabetes mellitus affects the patient-specific SI. The p-value less than 0.05 indicates that the result is significant.

The error of the two protocols (Malaysian ICU and STAR) were depicted in boxplot, as shown in Fig. 4, which is based on standard error of mean difference. STAR recorded lower measurement error (2–3%), in which this means that the virtual trials of simulated data are well-fitted with the ICING physiological model, to illustrate the actual glucose-insulin mechanism in critically ill patients. Thus, the virtual trial illustrates the true event of STAR if it is implemented in the Malaysian ICU setting.

Meanwhile, high error (5–110%) based on the Malaysian ICU data with some outliers in the boxplot indicates that the current Malaysian ICU BG protocols that separate insulin and nutrition administration need to be improved. On the other hand, ICING model embedded in STAR protocol considers simultaneous insulin and nutrition inputs, instead of having them separated, which reduces the fitting error significantly.

It is concluded that STAR protocol works well in the Malaysian ICU, which shows improvement as compared to the conventional IIT protocol. STAR virtual trial proves that hyperglycaemia issue is controllable and can be effectively solved. However, to maintain BG in targeted range, nutrition input has to work simultaneously with the insulin intake. The current Malaysian ICU protocol should be improved and further compliance study is needed to control hypoglycaemia. Moreover, the improvement of u_{en} in Eq. (7) of the ICING model will facilitate future works in any ICU settings. Besides, special patient classification of diabetic and nondiabetic has to be added into BG controller for the Malaysian ICU cohort. Particularly, diabetic is a major issue in Malaysia [13,15,16]. Thus, this should be considered in the modelling, to reduce the variability in SI. Futhermore, it will minimise the error of processed data that do not fit the physiological model simulation, especially in modelling endogenous insulin secretion for diabetic cohort.

5. Conclusion

The implementation of STAR in Malaysia helps to reduce hyperglycaemic rate and increase BG percentage within the targeted range (4.0–10.0 mmol/L), from 59.1% to 71.8% in diabetic patients and from 75.2% to 82.7% in nondiabetic patients. Several features in STAR (mathematical predictive model, insulin sensitivity) do not exist in the current BG protocol of the Malaysian ICU, they are indispensable to solve issues regarding BG and SI variabilities, especially in diabetic circumstance and the total treatment hour in diabetic cohort. In addition, STAR is more effective since it considers both insulin and nutrition in controlling BG level. However, the modelling of the endogenous insulin secretion should be validated to support clinical studies and therapy once STAR is imple-

mented in the Malaysian ICU. An automated nutrition controller (that refers to the Malaysian ICU nutrition protocol) should be designed based on the patient comorbidity to come up with the best glucose-insulin input in the Malaysian ICU setting.

Conflict of interest

The authors indicated no potential conflicts of interest.

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