

## The Effects of Insulin Infusion Protocol on the Glycemic Level of the Intensive Care Patients

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**Abstract:** Insulin infusion protocol is the standard protocol that has been practiced in Malaysia's intensive care unit (ICU) for controlling the hyperglycemia. Multiple sliding scale method of the insulin infusion protocol may drive conflict in selecting an appropriate scale to be applied to the patient. The objective of this paper is to analyse the blood glucose outcome of eight sliding scales insulin infusion protocol adopted in the Universiti Sains Malaysia Hospital (HUSM). A retrospective data of 78 ICU patients of HUSM were fitted using a validated glucose-insulin system to identify insulin sensitivity profiles of the patients. Then, these SI profiles were simulated on various scale protocols. The results obtained from this study showed that among eight scales, Scale 4 had the highest percentage of BG within the HUSM's target of 6.0 – 10.0 mmol/L. Scale 1 had the highest percentage of BG for the BG measurement more than 10.0 mmol/L while Scale 8 had the highest percentage of BG measurement of less than 6.0 mmol/L. However, none of the scale shown better performance than the current clinical practice. Furthermore, all of the eight scales had a more substantial number of BG measurement compared to the clinical. This study shows that Scale 2 and Scale 3 result in a similar outcome. Similarly, Scale 5 is almost the same as Scale 6. Thus, at least two sets of scale can be combined to reduce the number of scales. The reduction of scales consequently avoid confusion and helps the clinician in selecting the appropriate scale to be applied to the patients. From this study, it can be concluded that the HUSM protocol is a combination of scales. The scales may be shifted from one to another scale depending on patient condition and clinician judgement. A proper guideline for the scale shifting seems necessary to allow optimum glycemic management in the ICU.

*Keywords:* Glycemic control; critical care; model-based glycemic control; intensive care unit; HUSM.

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### 1. INTRODUCTION

Intensive care unit (ICU) patients often experience dynamic metabolism, which requires proper glycemic control and monitoring. According to the Malaysian National Health and Morbidity Survey, there was a 15% increase relatively in the prevalence of diabetes from the year 2011 to 2015 (*National Health & Morbidity Survey 2015*, 2015). Many protocols exist in managing the hyperglycemia, such as insulin infusion protocol and model-based control. Insulin infusion protocol consists of abundance protocols that are available in controlling the glycemic level (Van den Berghe, 2002; Goldberg *et al.*, 2004; Dilkhush *et al.*, 2005; Rea *et al.*, 2007). Most of the ICU in Malaysia control the glycemic level by

implementing the insulin infusion protocol that applies sliding scale method ('Blood Glucose Management in the Intensive Care Unit: Insulin Infusion Protocol', 2012).

Glycemic control protocol needs high monitoring as the outcome may vary between one patient to another due to different sensitivity and dynamic towards the medication. Additionally, the different cohort may react differently towards the insulin therapy adapted to the patients. Model-based controls such as Specialised Relative Insulin Nutrition Tables (SPRINT) and Stochastic Targeted (STAR) have shown to enhance the outcome of glycemic control. In particular, the effectiveness of the model-based methods have been investigated on the Malaysian cohorts via a virtual trial (Ahamad *et al.*, 2016; Razak *et al.*, 2016; Jamaludin *et al.*,

2018; Suhaimi *et al.*, 2018; Zafirah *et al.*, 2019) and indicated a promising result.

However, sliding scale is still considered as a primary method adopted in most of the ICUs in Malaysia even though this method may have a risk in the hypoglycaemia event (Guillermo, Andres and Dawn, 2007). Additionally, there are many other ICU from other countries that implement the sliding scale method for controlling the glycemic level including United States, United Kingdom, and India (Hemraj and Shaival, 2005; Golightly *et al.*, 2006; Hui, Kumar and Adams, 2012; Rickard *et al.*, 2016). In the sliding scale method, the infusion value and frequency of measurement usually are updated based on the current glycemic level. However, the scale may be selected based on the patient condition and glycemic level trend. Moreover, the change of scale mostly depends on clinician's judgement.

The glycemic target range for the critically ill patient is 7.8 – 10.0 mmol/L based on the American Diabetes Association (ADA) (Association, 2018). According to the International Diabetes Federation (IDF) (Colagiuri, 2012), the target range is 8.0 – 10.0 mmol/L, which is tighter compared to the recommendation made by ADA. The target range of 8.0 – 10.0 mmol/L made by the Malaysian Ministry of Health (MOH) is similar to the IDF recommendation (*Clinical Practice Guidelines, Management of Type 2 Diabetes Mellitus*. 5th edn., 2015).

The difference in BG target range affects the glycemic control protocol and treatment outcome. In reality, the dilemma of avoiding hyperglycemia and hypoglycaemia events may result in a selection of a broader target range. The aim of reaching the target as soon as possible may also contribute to the higher recommended dosage of insulin, which explained why one centre gives more insulin compared to another centre.

The main dispute of insulin given to the critically ill patient in HUSM's ICU was the scale that applied in insulin infusion protocol for particular current BG measurement. A clinician

may select the amount of insulin they prefer by using their clinical judgement, including their experience. However, the insulin amount might be different from one clinician to another. Thus, the patient outcome might be different following different selection of insulin therapy scale. This study analysed the blood glucose outcome among HUSM patients simulated using eight scales of insulin infusion protocol. A validated glucose-insulin system is used to identify insulin sensitivity profile of the patients.

## 2. METHODOLOGY

### 2.1 Clinical Data

78 retrospective clinical data were obtained from HUSM. ICU patients who received insulin therapy during hospital stay were selected. Clinical data required such as blood glucose measurement, insulin dosage, nutrition, heart rate, mean arterial blood pressure, respiratory rate, etc. Treatment data include inotropes, antibiotics, fluid resuscitation, etc.

The simulation was done on the retrospective clinical data for eight scales of HUSM's insulin infusion protocol. The insulin infusion was varied as in Fig. 1 and the feed was following the retrospective data. The output data from simulation were analysed and compared to the HUSM retrospective data.

### 2.2 Clinical Protocol

BG in HUSM is targeted to be controlled within 6.0 – 10.0 mmol/L. The BG value is monitored as soon as ICU admission. The BG measurement will be repeated within 1 hour if the BG value is more than 10 mmol/L. Insulin infusion will be started if the BG reading persistent more than 10 mmol/L. The BG level will be measured hourly until the result is within the target range of 6.0 – 10.0 mmol/L. The BG level will be monitored less regularly, every 4 hours, once the BG level is within the target. Fig. 1 shows the insulin infusion protocol of HUSM

| Blood glucose (mmol/l) | Scale 1 (U/h)                              | Scale 2 | Scale 3 | Scale 4 | Scale 5 | Scale 6 | Scale 7 | Scale 8 |
|------------------------|--|---------|---------|---------|---------|---------|---------|---------|
| ≥ 22                   | 3.0  | 4.0     | 5.0     | 6.0     | 7.0     | 8.0     | 10.0    | 11.0    |
| 18-                    | 2.5  | 3.5     | 4.0     | 5.0     | 6.0     | 6.0     | 8.0     | 9.0     |
| 14-                    | 2.0  | 3.0     | 3.0     | 4.0     | 5.0     | 5.0     | 6.0     | 7.0     |
| 12-                    | 1.5  | 2.5     | 2.5     | 3.0     | 4.0     | 4.0     | 4.0     | 4.0     |
| 10-                    | 1.0  | 2.0     | 2.0     | 2.0     | 3.0     | 3.0     | 3.0     | 4.0     |
| 8-                     | 1.0  | 1.5     | 1.5     | 1.5     | 2.0     | 2.0     | 2.5     | 3.0     |
| 6-                     | 0.5  | 1.0     | 1.0     | 1.0     | 1.5     | 1.5     | 2.0     | 2.0     |
| 5-                     | 0.5  | 0.5     | 0.5     | 0.5     | 1.0     | 1.0     | 1.5     | 1.5     |
| < 5                    | Stop IV insulin infusion and inform doctor |         |         |         |         |         |         |         |

Fig. 1. The insulin infusion protocol of HUSM

### 2.3 Glucose-Insulin Model

A glucose-insulin model by Chase *et al.* was used in this study to determine the insulin sensitivity profiles of the patient (Chase *et al.*, 2008). Several studies had been done in Malaysia's ICU also implemented this model (Jamaludin *et*

*al.*, 2016; Abdul Razak *et al.*, 2018; Suhaimi *et al.*, 2018). Fig. 2 shows the equations used for this model. The values of the constant parameter used in this glucose-insulin model are shown in Table 1 (Lin *et al.*, 2011; Fisk *et al.*, 2012). The insulin sensitivity was calculated from the equations and

identified every hour for each patient. Insulin sensitivity represents the sensitivity of the body cells to respond to insulin. Low insulin sensitivity may lead to hyperglycemia as the body cells do not absorb much glucose from the blood. However, high insulin sensitivity reduces blood glucose at a faster rate as the body cells can absorb glucose quickly.

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

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

$$\dot{I} = -n_K I - \frac{n_L I}{1+\alpha_I I} - n_I(1-Q) + \frac{u_{ext}(t)}{V_I} + (1-x_L) \frac{u_{en}}{V_I} \quad (3)$$

Where:

- G [mmol/L] = total BG concentration
- Q [mU/L] = effect of previously infused insulin
- I [mU/L] = plasma insulin
- $p_G$  [1/min] = patient endogenous glucose clearance
- $S_I$  [L/mU/min] = insulin sensitivity
- $V_G$  [L] = glucose distribution volume
- $V_I$  [L] = insulin distribution volume
- $P(t)$  [mmol/min] = external nutrition
- $EGP_b$  [mmol/min] = basal endogenous glucose production
- $CNS$  [mmol/min] = central nervous system glucose uptake

Fig. 2. Glucose-insulin model.

**Table 1. The value of constant parameters used in the glucose-insulin model.**

| Symbol     | Parameter                                  | Value               |
|------------|--|---------------------|
| $\rho_G$   | Patient endogenous glucose cleance         | 0.006/min           |
| $V_G$      | Glucose distribution volume                | 13.3 L              |
| $V_I$      | Insulin distribution volume                | 4.0 L               |
| EGP        | Basal endogenous glucose production        | 1.16 mmol/min       |
| CNS        | Central nervous system glucose uptake      | 0.3 mmol/min        |
| $x_L$      | First-pass liver extraction of insulin     | 0.67                |
| $n_I$      | Diffusion rate between I and Q             | 0.006/min           |
| $n_c$      | Interstitial insulin degradation base rate | 0.006/min           |
| $n_K$      | Kidney insulin clearance base rate         | 0.0542/min          |
| $n_L$      | Liver insulin clearance base rate          | 0.1578/min          |
| $\alpha_I$ | Insulin clearance saturation               | $1.7e^{-3}$ L/mU    |
| $\alpha_G$ | Insulin binding saturation                 | $\frac{1}{65}$ L/mU |

### 3. RESULTS AND DISCUSSION

The cumulative distribution function (CDF) of insulin sensitivity (SI) of HUSM patients is shown in Fig. 3. The median value of insulin sensitivity is 54.2 L/(mU.min), and the interquartile range is between 33.33 L/mU.min to 83.3 L/(mU.min). The insulin sensitivity for HUSM cohort is identified hourly. The identified SI acted as a metabolic profile of the patients and was used to simulate glycemic control protocols.

Table 2 shows the summary of BG measurements on a cohort and per-patient basis. HUSM had 3182 BG measurements clinically for the 78 patients, with an average of 41 BG

measurements per patient. For the simulation, Scale 7 produced the highest total number of BG measurement of 5770 with an average of 74 BG measurements per patient. Meanwhile, the lowest total number of BG measurement was Scale 4, which was 5568 and average of 71 BG measurements per patient. Scale 4 had the smallest percentage difference of 54.53% compared to the clinical result.

The clinical median BG for the whole cohort of HUSM was 9.4 mmol/L. Besides, simulation of Scale 1 resulted into median BG of 10.3 mmol/L, which was the highest among other scales. Scales 2, 3 and 4 gave resulted into a similar median BG, and interquartile range of 9.9 mmol/L and 6.8-10.8 mmol/L, respectively. The lowest median BG was on Scale 8 with 8.9 mmol/L. Scale 5 and Scale 6 resulted in a similar median BG of 9.5 mmol/L, which was the closest to the clinical value of HUSM.

The interquartile range of the blood glucose was 7.5 and 11.4 for the clinical value of the HUSM cohort. Additionally, the difference between the interquartile BG was 3.9. The highest IQR difference in BG was Scale 8 with 5.2. Meanwhile, the IQR for Scale 1 was 7.7 – 11.0 mmol/L, which resulted in the smallest IQR difference of 3.3 mmol/L compared to others. This indicates that Scale 1 able to control BG effectively compared to Scale 8.

The median insulin rate per patient was 0.8 U/hr administered clinically to the HUSM patients was shown in Table 2. Scale 8 gave the highest median insulin of 2.8 U/hr compared to other scales, with more than 3x of insulin given clinically. Scale 1 gave the nearest insulin with HUSM clinically, which was 0.9 U/hr. The percentage difference between Scale 1 and HUSM was 11.76%. Scales 2, 3 and 4 gave similar insulin of 1.5 U/hr, which is almost double the insulin given clinically. Additionally, the insulin for Scale 5 was similar to the insulin of Scale 6, which was 2.1 U/hr.

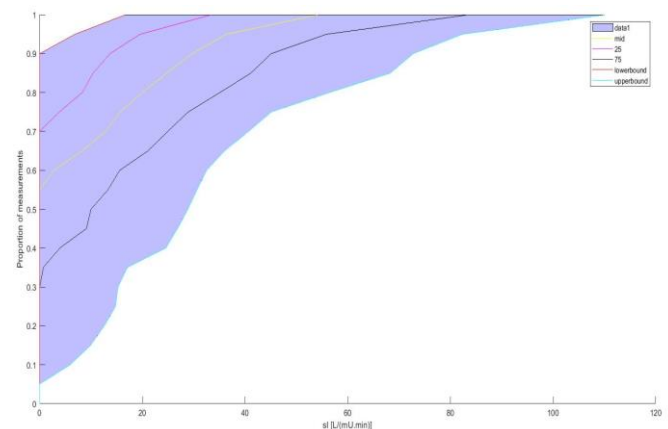


Fig. 3. Insulin sensitivity of HUSM cohort.

The finding from this study shows that by increasing 12.5% of insulin, the BG improvement was 9.6% as a result of Scale 1 protocol. The ratio of BG improvement to insulin increment for Scale 1 was 0.77, which is the highest compared to others. It shows that Scale 1 results in BG improvement with the given insulin. Besides that, the BG improved by 5.32% when the insulin increased to 87.5% following Scale 2 until Scale 4.

These scales gave 0.06 of BG improvement per insulin increment. Even though Scale 8 increased the insulin more than 3x of insulin administered clinically, the BG improvement was only 13.64%. The insulin used in Scale 8 was ineffective, as it only resulted in small BG improvement with the given amount of insulin.

From Table 2, the highest percentage of BG measurement within the target range of 6.0 – 10.0 mmol/L was the clinical data of HUSM with 50.31%, followed by Scale 4 with 31.61%. Scale 8 resulted in the highest percentage of BG measurement of less than 6.0 mmol/L of 29.59% compared to the clinical

data, which was 9.55%. Meanwhile, Scale 1 resulted in the highest percentage measurement of 54.58% at BG > 10.0 mmol/L compared to the clinical data, with 40.13%.

Scale 2 and Scale 3 resulted in similar percentage of BG < 6.0 mmol/L, 6.0 mmol/L ≤ BG ≤ 10.0 mmol/L, and BG > 10.0 mmol/L. Similarly, Scale 5 and Scale 6 also resulted in similar outcomes indicating that Scale 2 is nearly similar to Scale 3, and Scale 5 is nearly similar to Scale 6. Thus, eliminating the overlapped scale may also reduce confusion when selecting the appropriate scale to be applied to the patients.

**Table 2. Summary of blood glucose (BG) measurements on cohort and per-patient basis.**

|  | Clinical            | Simulated            |                      |                      |                      |                     |                     |                     |                     |
|--|---------------------|----------------------|----------------------|----------------------|----------------------|---------------------|---------------------|---------------------|---------------------|
|  |                     | Scale 1              | Scale 2              | Scale 3              | Scale 4              | Scale 5             | Scale 6             | Scale 7             | Scale 8             |
| Number of patients:                        | 78                  | 78                   | 78                   | 78                   | 78                   | 78                  | 78                  | 78                  | 78                  |
| Total number of BG measurement:            | 3182                | 5759                 | 5581                 | 5581                 | 5568                 | 5637                | 5637                | 5770                | 5714                |
| BG median (cohort) [IQR] (mmol/L):         | 9.4<br>[7.5 - 11.4] | 10.3<br>[7.7 - 11.0] | 9.9<br>[6.8 - 10.8]  | 9.9<br>[6.8 - 10.8]  | 9.9<br>[6.8 - 10.8]  | 9.5<br>[6.0 - 10.8] | 9.5<br>[6.0 - 10.8] | 9.2<br>[5.7 - 10.8] | 8.9<br>[5.6 - 10.8] |
| BG median per-patient [IQR] (mmol/L):      | 9.6<br>[8.7 - 10.4] | 10.3<br>[9.1 - 10.9] | 10.1<br>[8.8 - 10.8] | 10.1<br>[8.8 - 10.8] | 10.1<br>[8.7 - 10.8] | 9.8<br>[7.8 - 10.8] | 9.8<br>[7.8 - 10.8] | 9.8<br>[7.4 - 10.8] | 9.6<br>[7.3 - 10.7] |
| Median of insulin rate per-patient (U/hr): | 0.8<br>[0.3 - 1.4]  | 0.9<br>[0.8 - 1.0]   | 1.5<br>[1.3 - 1.7]   | 1.5<br>[1.3 - 1.7]   | 1.5<br>[1.3 - 1.8]   | 2.1<br>[1.7 - 2.4]  | 2.1<br>[1.7 - 2.4]  | 2.5<br>[2.1 - 2.7]  | 2.8<br>[2.4 - 3.2]  |
| % measurement BG < 6.0                     | 9.55                | 15.96                | 19.37                | 19.37                | 19.43                | 24.59               | 24.59               | 28.23               | 29.59               |
| % measurement 6.0 ≤ BG ≤ 10.0              | 50.31               | 29.47                | 31.46                | 31.46                | 31.61                | 30.80               | 30.80               | 29.20               | 29.87               |
| % measurement BG > 10.0                    | 40.13               | 54.58                | 49.17                | 49.17                | 48.96                | 44.62               | 44.62               | 42.56               | 40.53               |

Fig. 4 shows the graphs of CDF of BG for the whole cohort and BG median per patient for HUSM and all the insulin scales. From Fig. 4(A), the BG CDF for the whole cohort of HUSM and all simulated scales were varied between 4.0 mmol/L to 18.0 mmol/L. The CDF of BG for Scale 1 was almost overlapped to the clinical result. All the insulin scales were intersected with the clinical data at 10.8 mmol/L with a frequency of 70%. The CDF of BG for Scale 3 and Scale 4 were overlapped.

Per-patient analysis of the BG indicates that Scale 8 was the closest to the clinical result, particularly on the median of BG, as shown in Fig. 4(B). However, the 25<sup>th</sup> percentile was lower

and the 75<sup>th</sup> percentiles higher, indicating a broader range of BG for Scale 8. All the scales were overlapped within 70% - 80% of the CDF. Scale 3 and Scale 4 were also overlapped for the CDF of BG median per patient.

The CDF of insulin is shown in Fig. 5. The CDF of insulin for Scales 2, 3, and 4 were overlapped. Scale 1 provided the closest amount of insulin to the clinical data compared to other scales. This study shows that Scale 1 protocol was the nearest to the clinical results in terms of the cumulative distribution of insulin administered. However, Scale 1 required an additional 81% of BG measurement compared to the clinical, which may be unnecessary for clinical administration.

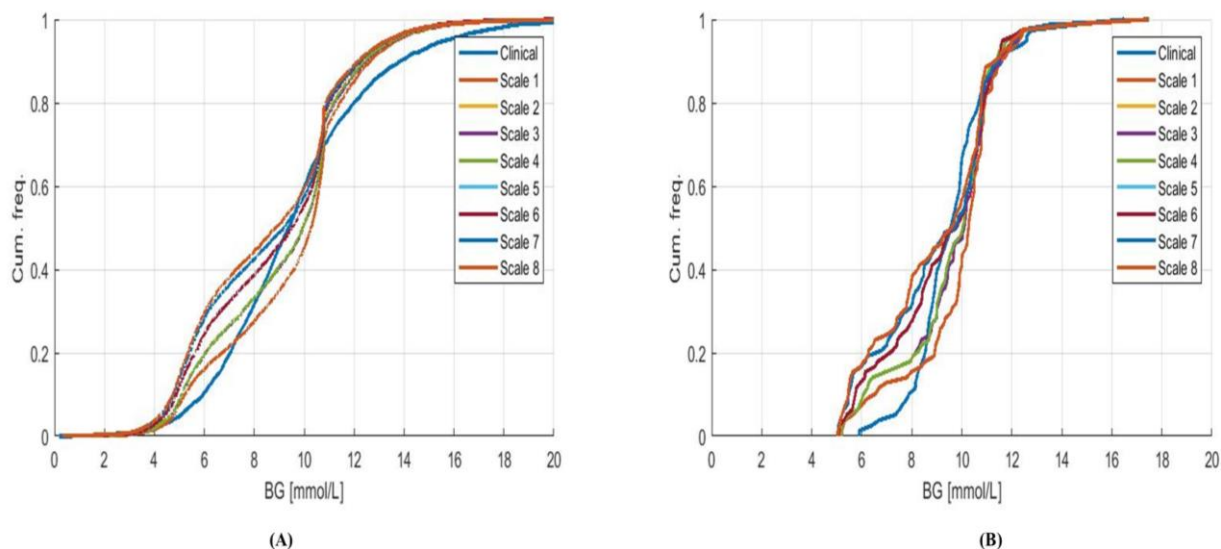


Fig. 4. Cumulative distribution function of (A) blood glucose for the whole cohort and (B) blood glucose median per patient.

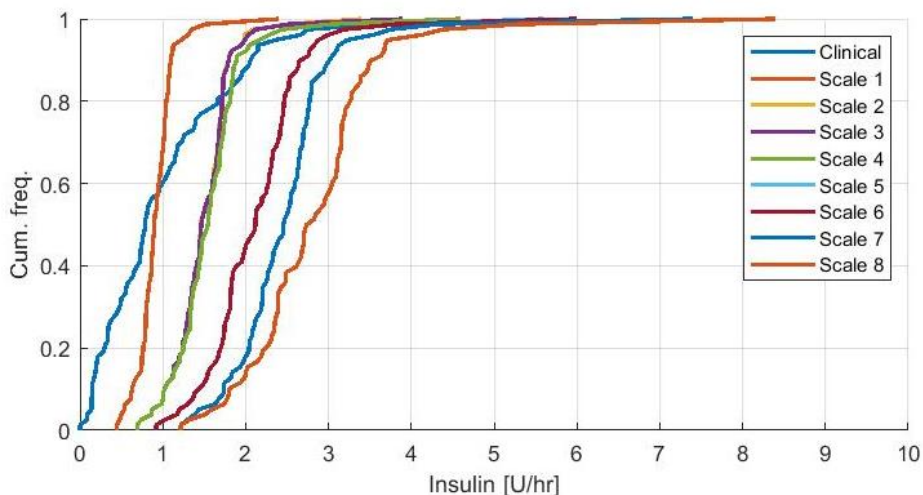


Fig. 5. Cumulative distribution function of insulin.

Within the limitation of this study, it is shown that the performance of current clinical protocol is better compared to the eight sliding scales adopted in the HUSM. Additionally, the highest percentage of BG measurement within the target was recorded by the clinical result, and no other scales were close to the clinical result. There might be a possibility of scale shifting within the treatment period. For example, a clinician may start with a lower scale and shift to a higher scale after a certain period based on the patient condition. Thus, what has been applied clinically in HUSM was a combination of scales, and not limited to only one scale method

From this study, it is suggested that Scale 2 can be combined with Scale 3 since they gave almost similar results. Similarly, Scale 5 and Scale 6 can also be matched to reduce the number of scale selection. Second, Scale 8 should be eliminated as the results are considered ineffective, where the patients were given high insulin but not giving impactful BG improvement. It is concluded that the HUSM protocol combines multiple scales, potentially a shifting phase between Scale 1, Scale 4,

and Scale 7 during a patient stay. With the combination of these scales, it could increase the insulin unit, hence improve the BG within the target.

#### 4. CONCLUSIONS

Comparing the eight scales of HUSM, Scale 4 had the highest percentage of BG within the target. However, Scale 4 is still not better than current clinical practice. Scale 1 had the highest percentage of BG measurement greater than 10 mmol/L, while Scale 8 had the highest percentage of BG measurement of less than 6 mmol/L compared to other simulated scales. It can be concluded that HUSM protocol is a combination of scales, where it shifts from one scale to another depending on patient condition and clinician experience. There is a necessity of scales shifting to avoid hyperglycemia and hypoglycemia in managing critically ill patients, as seen in this study. However, a reduction of scales number and a clear guideline of scale selection is necessary to avoid confusion. The application of continuous glucose monitoring may be suggested in future for confirming the better pattern of insulin sensitivity.

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