DEVELOPMENT OF COMPREHENSIVE GLYCEMIC CONTROLLER FOR CRITICALLY ILL PATIENTS WITH DIABETES MELLITUS AND NON-DIABETES MELLITUS

NUR JIHAN BINTI MOHD ZUKHI

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DEVELOPMENT OF COMPREHENSIVE GLYCEMIC CONTROLLER FOR CRITICALLY ILL PATIENTS WITH DIABETES MELLITUS AND NON-DIABETES MELLITUS

by

NUR JIHAN BINTI MOHD ZUKHI

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LIST OF UNITS AND SYMBOLS

%	Percent
g/hr	Grams per hour
L/mU.min	Liters per milliunit per minute
min^{-1}	Reciprocal minutes
mmHg	Millimeters of mercury
mmol/L	Millimoles per liter
mmol/min	Millimoles per minute
mU/L	Milliunits per liter
mU/min	Milliunits per minute
U/hr	Units per hour

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
APACHE	Acute Physiology and Chronic Health Evaluation
ATP	Adenosine Triphosphate
BG	Blood Glucose
CDF	Cumulative Distribution Function
DBSCAN	Density-Based Spatial Clustering of Applications with Noise
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
FiO_2	Fraction of Inspired Oxygen
GUI	Graphical User Interface
HbA1c	Glycated Hemoglobin
HREC	Human Research Ethics Committee
HUSM	Hospital Universiti Sains Malaysia
ICING	Intensive Control Insulin-Nutrition-Glucose
ICU	Intensive Care Unit
ID	Identification
IDF	International Diabetes Federation
IGFBP-1	Insulin-like Growth Factor-Binding Protein-1
IIT	Insulin Infusion Therapy
IL-1	Interleukin-1
IL-6	Interleukin-6
IV	Intravenous
MAP	Mean Arterial Pressure
MATLAB	Matrix Laboratory
MOH	Malaysian Ministry of Health
NICE-SUGAR	Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation
NKMI	No Known Medical Illness
Non-DM	Non-Diabetes Mellitus
PID	Proportional-Integral-Derivative

SC	Subcutaneous
S_I	Insulin Sensitivity
SIH	Stress-Induced Hyperglycaemia
SIRS	Systemic Inflammatory Response
SOFA	Sepsis-related Organ Failure Assessment
SPRINT	Specialised Relative Insulin Nutrition Tables
STAR	Stochastic TARgeted
TGC	Tight Glycaemic Control
TNF	Tumor Necrosis Factor
UMMC	University Malaya Medical Centre
VRIII	Variable Rate Intravenous Insulin Infusion
WCSS	Within Cluster Sum of Squares

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PEMBANGUNAN PENGAWAL GLISEMIK KOMPREHENSIF UNTUK PESAKIT KRITIKAL YANG MEMPUNYAI PENYAKIT DIABETES MELITUS DAN TANPA DIABETES MELITUS

ABSTRAK

Pesakit kritikal sering mengalami hiperglisemia akibat tekanan di Unit Rawatan Rapi (*ICU*), yang dikaitkan dengan peningkatan kesan klinikal yang buruk. Ketika ini, teknik skala luncur terapi infusi insulin (*IIT*) masih digunakan secara meluas di *ICU* untuk mengawal tahap glisemik, walaupun kelemahannya menyebabkan kejadian hipoglisemia dan kebolehubahan glisemik yang tinggi. Penyakit pesakit seperti hipotensi yang disebabkan oleh sepsis dan kecederaan paru-paru menyebabkan tekanan, yang mengakibatkan hiperglisemia. Objektif utama kajian ini adalah untuk membangunkan pengawal glisemik yang komprehensif untuk pesakit kritikal dengan diabetes *(DM)* dan tanpa diabetes *(non-DM)*. Kajian ini membangunkan pengawal glisemik berasaskan model untuk pesakit dengan diabetes dan tanpa diabetes, menggabungkan pembolehubah berpotensi untuk meningkatkan keberkesanan dan keselamatan *IIT* semasa. Kajian ini mengumpulkan data klinikal retrospektif pesakit *ICU* dengan intensif terapi insulin dan mempunyai sekurang-kurangnya 12 bacaan *BG* untuk mencipta pesakit maya dan mensimulasikan pengawal infusi insulin dengan menggunakan model *Intensive Control Insulin-Nutrition-Glucose (ICING)* untuk mengira S_I pesakit bagi setiap jam. Pengawal glisemik dicipta dengan pembolehubah berpotensi iaitu purata tekanan arteri (*MAP*) dan pecahan oksigen inspirasi (FiO_2), dikelompokkan menggunakan purata-K (*K-means*) dan teknik pengelompokan berasaskan ketumpatan spatial terhadap aplikasi dengan hingar (*DBSCAN*) bagi menentukan teknik yang dapat menghasilkan kelompok yang bersesuaian bagi kohort ini. Selain itu, pemboleh ubah S_I juga digunakan dalam

membangunkan pengawal yang dikategorikan. Keberkesanan dan keselamatan pengawal yang dibangunkan telah dibandingkan dengan data klinikal sebenar dan klinikal simulasi. Kajian ini menunjukkan bahawa S_I yang dikira oleh model *ICING* telah disahkan sebagai pembolehubah bebas untuk menilai rintangan insulin. Protokol infusi insulin skala gelongsor semasa didapati kadar insulin dan hasil glisemik adalah tidak penting, yang membawa kepada pengubahsuaian skala kepada empat skala, lantas mengurangkan kerumitan. Kajian mendapati bahawa *K-means* menghasilkan pengelompokan yang lebih terpiawai daripada *DBSCAN*, dengan empat kluster diperoleh untuk *MAP* dan FiO_2. Pengawal glisemik yang dibangunkan dengan julat sasaran 7.8 – 10.0 mmol/L dan tempoh bacaan *BG* selang dua jam selepas tiga bacaan *BG* berturut-turut dalam julat sasaran memberikan hasil yang optimum untuk pesakit diabetes dan tanpa diabetes. Syarat bagi dos insulin terawal adalah berbeza antara pengawal diabetes dan tanpa diabetes, tetapi keadaan bagi pemberian insulin berikutnya adalah sama. Pengawal yang dibangunkan dengan *BG*, *MAP*, dan FiO_2 meningkatkan keberkesanan dan keselamatan *IIT* semasa. Walau bagaimanapun, pengawal yang dibangunkan dengan *BG*, *MAP*, FiO_2, dan S_I, hanya meningkatkan prestasinya dengan peratusan tahap *BG* yang tinggi dalam julat sasaran. Oleh itu, IIT berkategori yang dibangunkan dengan *BG*, *MAP*, dan FiO_2 boleh digunakan dalam ujian klinikal untuk penilaian dan pelaksanaan selanjutnya dalam mengenal pasti dos insulin yang diperlukan untuk mengawal tahap glisemik dalam pesakit kritikal dengan peningkatan yang ketara.

DEVELOPMENT OF COMPREHENSIVE GLYCEMIC CONTROLLER FOR CRITICALLY ILL PATIENTS WITH DIABETES MELLITUS AND NON-DIABETES MELLITUS

ABSTRACT

Critically ill patients often experience stress-induced hyperglycaemia in the Intensive Care Unit (ICU), which is associated with the increased adverse clinical outcomes. Currently, the sliding scale technique of insulin infusion therapy (IIT) remains widely utilised in the ICU to control the glycaemic level, but its weaknesses cause high hypoglycaemia occurrences and glycaemic variability. The patient's diseases, like sepsis-induced hypotension and lung injury, cause stress, resulting in hyperglycaemia. The main objective of this research was to develop a comprehensive glycaemic controller for critically ill patient with diabetes mellitus (DM) and non-diabetes mellitus (non-DM). This study developed a model-based glycaemic controller for critically ill patients with diabetes and non-diabetes, incorporating potential variables to improve the efficacy and safety of current IIT. This study gathered retrospective clinical data of ICU patients with IIT and had at least 12 BG measurements to create virtual patients and simulate insulin infusion controllers by utilising the Intensive Control Insulin-Nutrition-Glucose (ICING) model to compute the patient's S_I hourly. Glycaemic controllers are designed with potential variables of mean arterial pressure (MAP) and fraction of inspired oxygen (FiO_2), clustered using K-means and density-based spatial clustering of applications with noise (DBSCAN) techniques to determine which technique produced appropriate clusters for this cohort. Besides, the S_I variable was also used in developing the categorised glycaemic controller. The developed controllers' efficacy and safety were compared to the actual clinical and simulated clinical data. This study demonstrated that the ICING model's

calculated S_I was verified as an independent variable for assessing insulin resistance. The current sliding scale insulin infusion protocol was found to be insignificant in insulin rates and glycaemic outcomes, leading to the modification of the scale to four scales, reducing complexity. The study found that K-means generated more standardised clusters than DBSCAN, with four clusters were obtained for MAP and FiO_2. The glycaemic controller developed with a target range of 7.8 – 10.0 mmol/L and a two-hour interval after three consecutive readings of BG within the target range provided optimal outcomes for diabetic and non-diabetic patients. The initial insulin dose conditions varied between diabetic and non-diabetic controllers, but the subsequent insulin administration conditions were similar. The developed controller with BG, MAP, and FiO_2 improved the efficacy and safety of current IIT. However, the developed controller with BG, MAP, FiO_2, and S_I, only enhanced its performance with a high percentage of BG levels within the target range. Therefore, the developed categorised IIT with BG, MAP, and FiO_2 can be utilised in clinical trials for further evaluation and implementation in identifying the insulin dose required to control the glycaemic levels in critically ill patients with the significant enhancement.

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Stress-induced hyperglycaemia (SIH) is common among critically ill patients during their stay in the intensive care unit (ICU). SIH occurs in ICU patients regardless of whether they have a history of diabetes. SIH is globally prevalent and is associated with an increased incidence of adverse clinical outcomes. SIH develops because of disease activating the body's stress response, which results in the production of stress hormones such as adrenaline and noradrenaline. These hormones can raise blood glucose (BG) levels by stimulating glycogenolysis, gluconeogenesis, and lipolysis influenced by counter-regulatory hormones and pro-inflammatory cytokines (Vedantam et al., 2022).

Counter-regulatory hormones such as catecholamines, cortisol, and growth hormone will disrupt glucose haemostasis by limiting insulin production and glucose absorption (Haring et al., 1986). Meanwhile, pro-inflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), and tumour necrosis factor (TNF) will increase insulin resistance (Hotamisligil, 1999). The state of restricted insulin activation and glucose absorption, along with significant insulin resistance, raises BG levels and leads to hyperglycaemia.

Insulin is a hormone that the body produces to control BG levels. Insulin stimulates the body's cells to absorb glucose and use it as energy. When excessive glucose levels in blood vessels are detected, beta cells in the pancreas release insulin (Gerich et al., 1976). Thus, the insulin sensitivity (S_I) of body cells is important in the control of BG levels. A low S_I implies that the cell is not responding appropriately to

insulin. Patients with poor S_I would most likely have high glucose levels and a proclivity for hyperglycaemia episodes during their stay in the ICU.

Appropriate glycaemic control should be applied to the ICU patients to control the hyperglycaemia events and reduce the nursing workload in the ICU. According to the Malaysian Registry of Intensive Care, the number of intensivists in Malaysia is around 40, which is about 0.2% per 100,000 populations. There are 3,749 ICU nurses in Malaysia who need to manage and monitor 70 – 75% of ICU occupancy (Geok et al., 2017; Nor, 2019). This indicates a high workload in the ICU among intensivists and nurses to monitor and take care of the ICU patients. More workloads may cause the staff to become fatigued, which leads to less efficiency and error in monitoring critically ill patients. This will make the ICU environment become under pressure, which may affect the patient's safety (Carayon & Gurses, 2017). The clinical workload may be reduced by modifying the interval of BG measurement (Uyttendaele et al., 2020).

Hence, it is crucial to control the hyperglycaemia events among critically ill patients to avoid more complications that lead to mortality. Most ICUs implement intravenous (IV) insulin infusion therapy (IIT) to control BG levels because insulin has a short half-life, allowing it to circulate and be cleared from the body quickly. The ability to make rapid adjustments to the insulin dose based on the patient's specific needs enables better control of hyperglycaemia and helps avoid the occurrence of hypoglycaemia events during therapy. Hence, IIT is more efficient in controlling BG levels with a lower incidence of hypoglycaemia (Tran et al., 2019). Even though IIT is preferable for controlling BG levels, the sliding scale based on IIT is implemented in Malaysia's ICUs resulted in more hypoglycaemia events during the insulin treatment.

However, the current sliding scale consists of eight scales and a one-size-fits-all protocol, which is applied to all ICU patients without taking into consideration the patients' diabetes history and other factors such as insulin resistance (Malaysian Society of Intensive Care, 2019). However, studies showed that the main drawback of the sliding scale is high hypoglycaemia occurred during the IIT (Almagthali, Alsohimi, Alkhalaf, Al Sulaiman, & Aljuhani, 2024; Golightly, Jones, Hamamura, Stolpman, & McDermott, 2006). The finding from Younis et al. (2019) showed that 8% of the hypoglycaemia events occurred using a paper-based sliding scale. The occurrence of hypoglycaemia also may lead to more complications for the patients and is also associated with an increased mortality rate in the ICU (Egi et al., 2010).

Many scales may lead to complex therapy and be time-consuming for the nurses in controlling the glycaemic levels (Razak et al., 2018). Moreover, this sliding scale also led to confusion, as some scales contained similar insulin doses, which a study showed resulted in insignificant glycaemic outcomes (Zukhi et al., 2020). Besides, this sliding scale only considers the BG levels in deciding the insulin dose to be administered to the ICU patients. Glycaemic control in the ICU is still refined as hyperglycaemia is related to adverse outcomes such as infections and mortality. Studies suggested considering the diabetic background and other factors to be utilised in the IIT (Ma et al., 2022; Prigeon et al., 1996; Suhaimi et al., 2010).

Currently, the model-based glycaemic controller has been utilised in the ICU, and some studies have used it to regulate the glycaemic level among ICU patients (Abu-Samah et al., 2019; Athirah et al., 2024; Uyttendaele et al., 2020). A model-based glycaemic controller is a glycaemic controller that implements a computerised method that captures patients' insulin sensitivity and patients' metabolic, and thus allows access to the patients' glycaemic levels directly (Chase et al., 2007; Lonergan

et al., 2006). These are the advantages of the model-based controller that are unavailable when using the sliding scale method. The Intensive Control Insulin-Nutrition-Glucose (ICING) model is the clinically validated model that enables calculating the patients' S_I and helps in determining the insulin dose and nutrition in controlling the glycaemic levels (Lin et al., 2011). Many glycaemic controller implement this model to control glycaemic levels in the ICU (Abu-Samah et al., 2019; Athirah et al., 2024; Uyttendaele et al., 2020).

Many variables affect the BG readings of ICU patients directly or indirectly, such as nutrition, medication, mean arterial pressure (MAP), fraction of inspired oxygen (FiO_2), etc. MAP is a very important parameter for vital signs that every doctor monitor in every patient. MAP contributes to the pressure that the body needs to keep perfusing all the tissue in the body, which includes tissue at the heart, lung, and kidney, which are the vital organs (Demers & Wachs, 2023). The study found that the MAP exhibits a positive correlation with diabetes (Wu et al., 2022). Low MAP, which refers to the hypotension case, will cause stress to the patient and indirectly increase the BG levels with high insulin resistance, low insulin secretion, and poor perfusion of the glucose to the liver. The minimum MAP as per the guideline currently is 65 mmHg (Evans et al., 2021). The MAP < 65 mmHg is regarded as the guideline for sepsis-induced hypotension (Singer et al., 2016). The study showed that the MAP more than 65 mmHg has been related to lower short-term mortality (Zhong et al., 2023).

Meanwhile, the fraction of inspired oxygen (FiO_2) is the oxygen that has been administered into the lung of the patient. The patient with respiratory failure needs extra oxygen to maintain the oxygen in their blood in between the range of 60 – 100 mmHg (Grensemann, Fuhrmann, & Kluge, 2018). In hospitals, oxygen is one of the commonly drug that has been used without appropriate control and prescription. This

might be the potential to be given an overdose by the doctor. The patient with lung injury needs the oxygen supply of $FiO_2 > 0.35$ (Gajic et al., 2011; Trillo-Alvarez et al., 2011). Low and high oxygen supply also can lead to stress to the body, which stimulates stress hormones and counter-regulatory hormones to be secreted (Damiani, Donati, & Girardis, 2018; Dyson et al., 2014). These hormones will cause increased insulin resistance and reduced insulin secretion that leads to hyperglycaemia.

In developing the comprehensive glycaemic controller for critically ill patients, the diabetic background of the patients and potential variables should be considered to improve the efficacy and safety of the current IIT. Virtual patients and virtual trials are needed to assess the current clinical protocol and develop the glycaemic controller, where the ICING model can be utilised. The developed glycaemic controller should give the optimal outcomes in order to control the glycaemic levels without jeopardising its safety with the high hypoglycaemia occurrence.

1.2 Research Problem

Hyperglycaemia is highly associated with increases in adverse clinical outcomes. In the ICU setting, the occurrence of the hyperglycaemia was 28.6% - 50% (Baker et al., 2020; Levetan, Passaro, Jablonski, Kass, & Ratner, 1998; Plummer et al., 2014). Although Malaysia ICU implemented IIT based on a sliding scale, yet the main drawback of the sliding scale is uncontrollable hypoglycaemia incidences, which can cause sudden mortality among critically ill patients (Almagthali et al., 2024; Golightly et al., 2006). Besides, the sliding scale causes more glycaemic variability that leads to a longer time to reach the target range (Clergeau et al., 2017). Moreover, the sliding scale consists of eight scales, which are complex and cause confusion for the nurses. Surveys conducted among Malaysian ICU staff revealed that the sliding

scale protocol is widely used, it is often perceived as complex and time-consuming (Razak et al., 2018). In addition, some scales have similar insulin doses, which have insignificant glycaemic outcomes, which can lead to confusion (Zukhi et al., 2020).

Furthermore, the current sliding scale used in the ICU is a one-size-fits-all protocol that applies to any category of ICU patients without looking for their diabetic background. Thus, it is required to develop a BG control that takes into account the safety of the patients and prevents hypoglycaemia events by considering the diabetic information of the ICU patients and other potential factors that affect the BG levels, as suggested from previous studies (Ma et al., 2022; Prigeon et al., 1996; Suhaimi et al., 2010).

In addition, MAP is a critical metric for vital indicators that all physicians monitor in all patients. The research conducted by Wu et al. (2022) discovered that the MAP has a positive association with diabetes. This study demonstrated a significant positive association with diabetes when the MAP is < 100 mmHg. Therefore, the inclusion of MAP in the IIT could potentially control the glycaemic levels. Moreover, MAP demonstrates the most significant correlation with ICU mortality, necessitating monitoring (Khanna et al., 2023).

Furthermore, the glucose metabolism will be altered if there is stress in the body, which releases stress hormones and counter-regulatory hormones. Counter-regulatory hormones, including cortisol, growth hormone, and catecholamines, will impair glucose haemostasis by inhibiting insulin secretion and glucose absorption through the simulation of glycogenolysis, gluconeogenesis, and lipolysis (Haring et al., 1986; Vedantam et al., 2022). Patients with sepsis-induced hypotension will experience hyperglycaemia as they have high insulin resistance due to the increased production of counter-regulatory hormones that leads to the elevation of BG levels

(Hassan, Badr, Al-Ashker, & Ahmed, 2021). Additionally, Walia and Sutcliffe (2002) reported the hyperglycaemia correlate with elevated mortality within the patients group with the lowest MAP was 40 mmHg or less.

Moreover, critically ill patients frequently experience acute respiratory failure, which includes lung injury that necessitates oxygen support during their ICU stay. Consequently, oxygen will be delivered to the patient's lung as indicated by FiO_2. The patient exhibits respiratory failure due to viral agents and infections, such as pneumonia. The MOH reports that pneumonia is the leading cause mortality in Malaysia, according to the most recent statistics (*Statistics on Causes of Death Malaysia, 2024*, 2024). Oxygen is frequently administered without proper regulation and prescription in the hospitals, which may present the possibility of receiving an overdose from the physician. $FiO_2 > 0.35$ is considered one of the indicators used to assess the prognosis score for lung damage (Gajic et al., 2011; Trillo-Alvarez et al., 2011).

Low and high oxygen levels can cause physiological stress, leading to the secretion of stress hormones and counter-regulatory hormones (Damiani, Donati, & Girardis, 2018; Dyson et al., 2014). These hormones can increase insulin resistance and decrease insulin secretion, and then cause hyperglycaemia. Moreover, patients who required the oxygen supply commonly used corticosteroids, which worsened the hyperglycaemia, and more insulin administration is needed to manage the fluctuation of the glycaemic levels (Becker et al., 2020; Group, 2021; C. Pretty et al., 2011).

1.3 Research Objectives

The main objective of this study is to develop a comprehensive glycaemic controller for critically ill patients with DM and non-DM.

This study embarks on the following specific objectives:

1) To assess the current blood glucose control system in the Malaysia ICU and reduce its complexity by creating virtual patients and conducting virtual trials with the implementation of the ICING model.
2) To implement potential variables in the glycaemic controller for DM and non-DM by clustering the variables into effective clusters with K-Means and DBSCAN techniques.
3) To design and develop the categorise protocols with the proposed variables by considering the improvement of efficacy and safety of the current blood glucose control.
4) To validate the improvement in efficacy and safety of the glycaemic controller for managing ICU patients by conducting the virtual trials with the new cohort and incorporating S_I changes into the glycaemic controller.

1.4 Scope of Research

This study developed a comprehensive glycaemic controller for DM and non-DM patients in the ICU by introducing potential variables in the glycaemic controller. Virtual trials were conducted in this study using virtual patients generated from data obtained from ICU charts to evaluate the dependency of virtual patient on the protocol implemented. The dataset from May 2017 to April 2018, with a BG target of 6 – 10 mmol/L was used for creating virtual patients and evaluating virtual trials on the sliding scale IIT. Moreover, the current IIT protocol employed in the ICU was assessed

using a new dataset from January to November 2020, with the BG target range of 8 – 10 mmol/L, to reduce its complexity. Additionally, this dataset served as the basis for developing the categorised IIT in this study. The glycaemic controller developed in this study is categorised for DM and non-DM with the potential variables BG, MAP, and FiO_2. Two clustering techniques (K-means and DBSCAN) were implemented in this study to determine the most suitable technique for this cohort. The clusters derived from the optimal technique were subsequently utilised in designing the glycaemic controller. The improvement in efficacy and safety of the developed glycaemic controller was assessed by comparing the outcomes with actual and simulated clinical protocols. The efficacy of the protocol is observed in the timeframe for the BG levels to be within the target range, and the occurrence of hyperglycaemia and BG levels within the target range. Meanwhile, the safety of the protocol is observed in the timeframe to reach the target range and the hypoglycaemia occurrence. S_I changes were also introduced in the protocol, along with BG, MAP, and FiO_2, to observe the improvements in the efficacy and safety of the newly developed protocol.

1.5 Significance of Research

This study will benefit the community in terms of managing hyperglycaemia in the ICU. A model-based glycaemic controller developed from this study is expected to describe the physiological dynamics of glucose-insulin behaviour and become a significant tool for managing hyperglycaemia in real time. The model-based glycaemic controller will ensure the patient's safety by considering the incidence of hypoglycaemia and the timeframe for reaching the target BG range. Thus, the mortality rate in critically ill patients can be reduced. This controller will also help doctors and nurses manage critically ill patients in real-time which makes ICU management more

efficient and effective. By applying this model-based glycaemic controller, the management of hospitals in Malaysia is moving towards a categorised and precision medicine approach.

1.6 Thesis Outline

Chapter 1 introduces the background of this study and the problems that led to this research. Furthermore, the research objectives, research scope, and significance of this research are described in this chapter.

Chapter 2 presents the literature review for this research which introduces the diabetic background of critically ill patients. Furthermore, the BG regulation that led to hyperglycaemia and hypoglycaemia are explained in this chapter. Moreover, the techniques used in managing the glycaemic level that exists are discussed in this chapter including the model-based glycaemic controller.

Chapter 3 describes the assessment of the current clinical protocol and reduce its complexity. The assessment is conducted with the creation of virtual patients and virtual trials using the clinical data collected from Hospital Universiti Sains Malaysia (USM). Moreover, the creation and validation of the virtual patients developed in this research are also discussed in this chapter.

Chapter 4 explains how the clusters obtained for potential variables were used in this study by implementing the K-means and DBSCAN techniques. Besides, this chapter also shows the correlation between the potential variables used in this study with the BG levels.

Chapter 5 devotes the development of a new categorised protocol for critically ill patients with DM and non-DM, by utilising the potential variables of MAP and

FiO_2. Additionally, this chapter also listed the criteria and design for developing the categorised IIT.

Chapter 6 reports the findings of the evaluation of the categorised IIT developed in this study with new DM and non-DM cohorts. Different cohorts are used in this chapter to assess the applicability and performance of the newly developed protocols. Moreover, S_I values were introduced in the categorised glycaemic controller to improve their efficacy and safety. The S_I changes were classified and utilised in designing new categorised IIT.

Chapter 7 presents graphical user interface (GUI) designed for a mobile application (Glyco Guide) to implement the developed categorised protocols. The design processes were explained to ensure Glyco Guide is readily to be used in clinical settings.

Chapter 8 concludes this research together with reflections on the limitations of this study and recommendations for future studies that are expected to be achieved from this research.

1.7 Research Flow Outline

The research flow outlined in Figure 1.1 illustrates the progression of the study and the interconnections between chapters to achieve the research objectives.

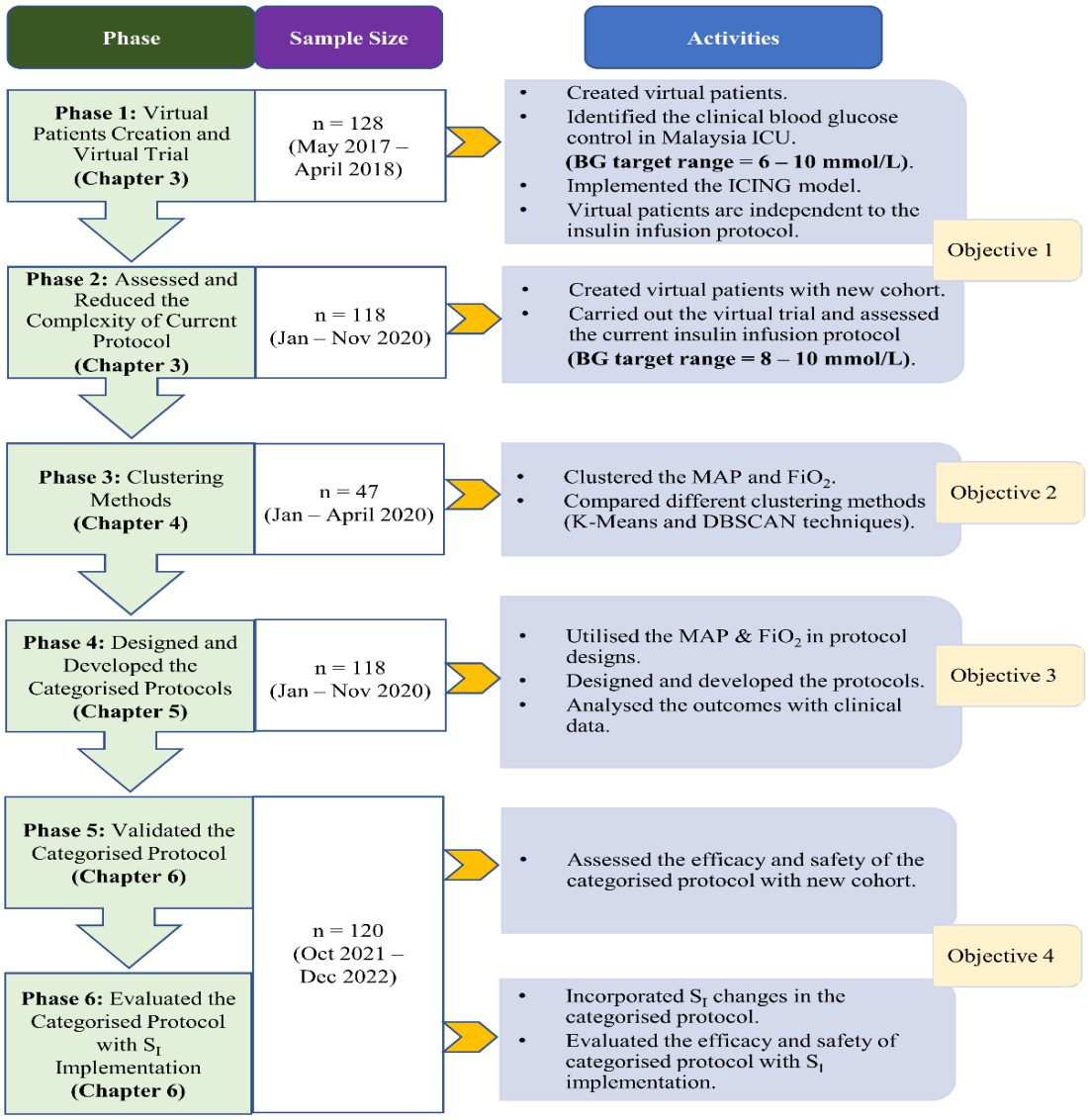

Figure 1.1 The diagram of research flow.

CHAPTER 2

LITERATURE REVIEW

This chapter introduces glycaemic control and its effect on hyperglycaemia and hypoglycaemia events among ICU patients. Besides, current insulin infusion protocols that implemented as sliding scale-based method applied in the Malaysia ICU will be a preamble. Moreover, the validated model that is implemented in this study will be introduced in this chapter. This model is able to capture the S_I of each patient that is able to illustrate the patient's condition. This chapter also discusses the metabolic effects of hyperglycaemia and scoring systems among critically ill patients. The clustering techniques to classify the parameters are discussed in this chapter.

2.1 Insulin and Glucagon Regulation

The regulation of insulin and glucagon is visualised in Figure 2.1. Micro molecules are formed after eating, such as glucose, fat, and amino acids in the intestine. Glucose will be absorbed by the blood which then stimulates the secretion of insulin from the pancreas as there are increments of glucose in the blood. The pancreas consists of alpha, beta, and delta cells which they will secrete different hormones in the body. Alpha cells secrete glucagon hormones, while beta cells secrete insulin hormones, which are needed for controlling BG levels. The secretion of insulin promotes the uptake of glucose from the blood into the liver and converts it to become glycogen. Then, the glycogen in the form of energy will be stored in the tissue cells (J. E. Gerich et al., 1976).

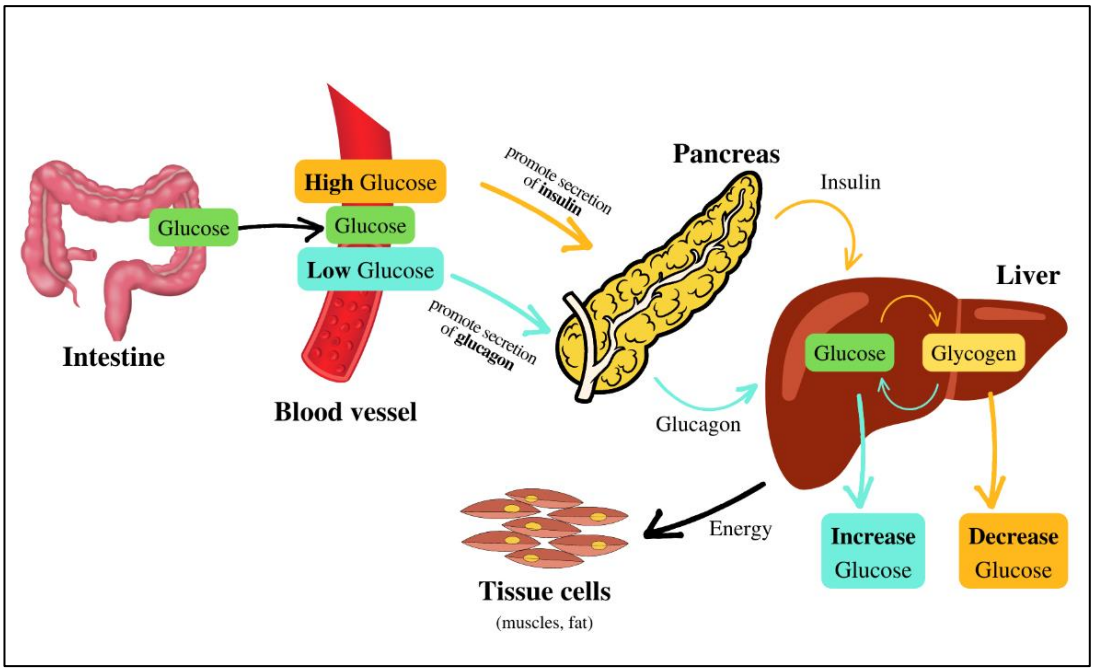

Figure 2.1 The schematic diagram of insulin and glucagon regulation in controlling the blood glucose levels in the body.

In the homeostasis of BG levels in the body, the pancreas plays an important role to stimulate the insulin and glucagon formulation. When the condition of high BG also known as hyperglycaemia, the pancreas will be promoted to secrete insulin and form glycogen in the liver, which will reduce the BG level. The glucagon hormones will be released when low BG (hypoglycaemia) happens, which will stimulate glucose formation in the liver to increase the BG level (J. E. Gerich et al., 1976).

2.1.1 Hyperglycaemia

Hyperglycaemia events occur when the BG readings indicate a value greater than 10.0 mmol/L among critically ill patients who need IIT to control their BG level (American Diabetes Association, 2018a). However, other studies specify hyperglycaemia as a BG measurement greater than 11.1 mmol/L (Montori et al., 2002). ICU patients with DM together with hyperglycaemia were defined with glycated haemoglobin (HbA1c > 6.5%) (American Diabetes Association, 2018b; Singh et al., 2018).

Among critically ill patients, the stress hormones released will increase the concentration of counter-regulatory hormones which leads to the increment of hepatic glucose production (Haring et al., 1986). Meanwhile, the glucose uptake decreased with the increment of counter-regulatory hormones concentration (Haring et al., 1986). Besides, insulin hormone production will reduce and be inadequate to respond to glucose production which will then elevate BG levels (Montori et al., 2002; Surwit et al., 1992).

Hyperglycaemia may lead to adverse outcomes including an increase in the length of stay, organ failure, sepsis, and the mortality rate in the ICU (Joint British Diabetes Societies, 2014; WHO, 2006). The mortality rate was driven by the BG outcome, which will be increased by 75% per 2.8 mmol/L BG increment (Vincent et al., 2002). Moreover, uncontrolled hyperglycaemia may cause diabetic ketoacidosis (DKA) which is an indication of insulin deficiency. DKA among ICU patients may cause high mortality and morbidity which need attentive treatment that balance the benefit and the risk to the patients (Health and Social Care Information Centre, 2012; Zukhi et al., 2022).

Thus, it is vital to control the BG levels among critically ill patients to avoid unpredicted complications. Insulin therapy was suggested to have the capability to decrease the morbidity and mortality rate among ICU patients (Hassan et al., 2021; Robba & Bilotta, 2016). There are various methods for insulin therapy including sliding scale-based (George et al., 2015; Malmberg et al., 1995; Markovitz et al., 2002; Shetty et al., 2012), model-based glycaemic controllers (Chase et al., 2007; Lin et al., 2008), and proportional-integral-derivative (PID) control (Chee et al., 2003).

2.1.2 Hypoglycaemia

Hypoglycaemia is the condition when the BG levels are low, which stimulates the secretion of glucagon hormones and leads to glucose formation in the liver to increase the BG level (J. E. Gerich et al., 1976). Hypoglycaemia arises from impaired regulation of counter-regulatory hormones, inadequate supply of counter-regulatory hormones, inadequate carbohydrate consumption, and increased circulating insulin levels resulting from excessive insulin secretion or during IIT (American Diabetes Association, 2018b; Gerich, Davis, & Lorenzi, 1979; Rizza, Cryer, & Gerich, 1979).

Hypoglycaemia occurs when the BG levels are less than 3.9 mmol/L, which is known as level 1. Meanwhile, the BG levels less than 3.0 mmol/L are classified as level 2, which is also called clinically significant hypoglycaemia (Agiostratidou et al., 2017). The level 3 is called severe hypoglycaemia with the BG levels less than or equal to 2.2 mmol/L (Agus et al., 2017; American Diabetes Association, 2018b). The severe hypoglycaemia events can lead to adverse outcomes including mortality.

The treatment for the hypoglycaemia (level 1) is giving the glucose (15 – 20g) for the conscious individual (American Diabetes Association, 2018b). Meanwhile, the hypoglycaemia (level 2) is recommended to give glucagon (American Diabetes Association, 2018b). Otherwise, for the patients undergoing the IIT, it is recommended to increase the BG target range to prevent hypoglycaemia events (American Diabetes Association, 2018b). Younis et al. (2019) found that 8% of hypoglycaemia events occurred with the use of paper-based sliding scale. Therefore, it is crucial to develop the glycaemic controller by taking into consideration the BG target range to reduce the frequency of hypoglycaemia during the IIT.

2.2 Glucose Control

It is important to control the glucose level among critically ill patients to circumvent more serious complications. The guideline by the American Diabetes Association (ADA) for controlling hyperglycaemia using conventional IIT among ICU patients is 7.8 – 10.0 mmol/L, while 8.0 – 10.0 mmol/L is recommended by the International Diabetes Federation (IDF) and the Malaysian Ministry of Health (MOH) (American Diabetes Association, 2018a; Ceriello & Colagiuri, 2008; Ministry of Health Malaysia, 2015; Moghissi et al., 2009). Currently, MOH recommends the target range for the BG to be controlled is similar to the ADA starting in 2020 (Ministry of Health Malaysia, 2020a, 2020b). It is crucial to control the BG levels to be within the target range without the oversight of hypoglycaemia events. The studies found that the BG target of less than 8.0 mmol/L was ample for controlling hyperglycaemia with a low risk of hypoglycaemia (Al-Tarifi et al., 2011; Finney et al., 2003). Hence, the appropriate BG target should consider the patients' diabetic background and other factors to make IIT more effective and safer for ICU patients.

Controlling hyperglycaemia among ICU patients, while avoiding hypoglycaemia events is crucial. There are many techniques to control hyperglycaemia, but some approaches have been associated with high hypoglycaemia episodes among ICU patients. Hypoglycaemia may lead to a mortality rate among critically ill patients. Studies have shown that managing hyperglycaemia episodes by implementing tight glycaemic control (TGC) gave a promising result in controlling the hyperglycaemia (Finfer et al., 2009; Kopecký et al., 2013). Subsequently, TGC also prevents hypoglycaemia events, which attributed to reducing the mortality rate in the ICU (Berghe et al., 2006, 2001).

2.2.1 Tight Glycaemic Control

TGC is an IIT that tightly controls the BG within the target range of 4.4 – 6.1 mmol/L (Berghe et al., 2001). There were quite a few differences in the target range between IIT and conventional insulin therapy. Studies found the mortality rate among ICU patients was reduced with the TGC (Berghe et al., 2006, 2001). The findings led to the TGC application in the ICU setting in controlling glycaemic levels.

The research done by Lanspa et al. (2013) found that TGC among critically ill patients with diabetes is able to reduce the mortality rate in the ICU. However, the mortality rate among non-diabetes ICU patients increased with TGC. Additionally, some studies implemented the Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) as TGC (Finfer et al., 2009; Tanner, 2009). The conceptual framework of the NICE-SUGAR trial emphasised the balance between treating hyperglycaemia and preventing hypoglycaemia with findings indicating an increment in the mortality rate and severe hypoglycaemia events when implementing the TGC compared to conventional glucose control with the BG target range of 8.0 – 10.0 mmol/L (Finfer et al., 2009; Tanner, 2009). Therefore, the studies highlighted the significance of customised glucose treatment, including insulin medication and continuous monitoring, in order to improve the glycaemic outcomes.

The mortality rate is also associated with the length of stay of critically ill patients in the ICU. The ICU patients who stay three days and received the IIT will avail the mortality while the patients with shorter stays will have a higher rate of mortality (Berghe et al., 2006; Wilson, 2007).

Moreover, the insulin dose administered to the ICU patients from TGC was higher than conventional (Tanner, 2009). Hence, the TGC employment should consider the insulin dose that will impact on controlling the BG levels without wasting

the insulin usage as it will increase the cost and make the TGC more effective in lessening the hypoglycaemia episodes.

Furthermore, TGC should take into consideration the patient's insulin sensitivity and patients' variability when deciding the target to be applied among ICU patients (Lanspa et al., 2013; Suhaimi et al., 2010). Patients with comorbidities will react differently to the IIT they receive. Thus, a different group of patients demands a different target or therapy to make insulin treatment more effective (Wilson, 2007).

2.3 Sliding Scale-Based Method

The sliding scale method is the conventional IIT that was applied in the ICU to control BG. The sliding scale is basically a paper-based protocol which is the chart of the insulin dosage guidelines to be administered to the patients. This method was pioneered by Ellin Joslin (1937), and then the sliding scale was evolved by other researchers based on the BG outcomes, hypoglycaemia episodes, and the efficient amount of insulin dose to be administered to critically ill patients (Lukens, 1965). The sliding scale and the conditions for moving the sliding scale are different among centres based on their insulin infusion protocol. Moreover, the number of scales and the BG measurement interval are also different among centres. There were several sliding scales for the insulin infusion protocols including Variable Rate Intravenous Insulin Infusion (VRIII), Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI), and Yale insulin infusion protocol (George et al., 2015; Malmberg et al., 1995; Markovitz et al., 2002; Shetty et al., 2012).

The advantage of a sliding scale is one of the IIT methods that is convenient, has a direct value of insulin dosage, and is easy to apply. Furthermore, the implementation of the sliding scale is not stringent and allows nurses to control the

BG level. Sometimes the nurses need the doctor's intervention due to the patient's condition or the prolonged IIT, which needs an exceptional insulin dose.

Nonetheless, the disadvantages of the existing sliding scale are fit for all ICU patients without taking into consideration the patient's diabetic background, feed, patient's insulin sensitivity, and other potential variables that affect the BG level. Moreover, the sliding scale method is unable to control the hypoglycaemia episodes while controlling the hyperglycaemia events among ICU patients. This incident may also cause death among ICU patients (Browning & Dumo, 2004; Zaman et al., 2014).

Fortunately, there were evolvements in the sliding scale method including the computerisation of the insulin sliding scale to reduce human error, improve efficiency, and reduce hypoglycaemia episodes. A computerised sliding scale is able to standardise the time interval of the insulin administration and reduce the calculation errors involving glucose intake, insulin sensitivity, etc. Studies found promising outcomes in which the computerised sliding scale was able to reduce severe hypoglycaemia, reduce hyperglycaemia, and increase the number of BG within the target range (Dortch et al., 2008; Marvin et al., 2013).

2.3.1 Sliding Scale in Malaysia

The sliding scale of the insulin infusion protocol from the Ministry of Health Malaysia (MOH) & Malaysian Society of Intensive Care ICU Protocol (2012) is shown in Table 2.1. In 2012, the BG target range was 6.0 – 10.0 mmol/L and then changed to 8.0 – 10.0 mmol/L. After that, the target of 7.8 – 10.0 mmol/L was recommended by MOH starting in the year 2020, as recommended by the American Diabetes Association and the American Association of Clinical Endocrinologists (Malaysian Society of Intensive Care, 2019; Ministry of Health Malaysia, 2020b).

Table 2.1 Sliding scale from Ministry of Health Malaysia & Malaysian Society of Intensive Care ICU Protocol.

Blood glucose (mmol/L)	**Scale 1 (U/h)**	**Scale 2**	**Scale 3**	**Scale 4**	**Scale 5**	**Scale 6**	**Scale 7**	**Scale 8**
≥ 22.1	3.0	4.0	5.0	6.0	7.0	8.0	10.0	11.0
18.1 – 22	2.5	3.5	4.0	5.0	6.0	6.0	8.0	9.0
14.1 – 18	2.0	3.0	3.0	4.0	5.0	5.0	6.0	7.0
12.1 – 14	1.5	2.5	2.5	3.0	4.0	4.0	4.0	5.0
10.1 – 12	1.0	2.0	2.0	2.0	3.0	3.0	3.0	4.0
8.1 – 10	1.0	1.0	1.5	1.5	2.0	2.0	2.5	3.0
6.1 – 8	0.5	1.0	1.0	1.0	1.5	1.5	2.0	2.0
4.1 – 6	0.5	0.5	0.5	0.5	1.0	1.0	1.5	1.5
< 4	**Cease IV insulin infusion and inform doctor**							

The IIT starts once the BG is more than 10.0 mmol/L and starts with Scale 2. The scale will be moved to the first right column with a higher insulin dose when the current BG level is the same or higher than the previous BG level. Likewise, the scale will move to the first left column if the BG level is within 4.0 – 6.0 mmol/L. Otherwise, the scale will be maintained in the same column when the BG is within the target range. The BG is measured hourly during the treatment period until the BG reaches the target range for two hours, then the BG is measured 2 – 4 hourly. Moreover, the nurse should stop the insulin infusion and inform the doctor if the BG reading is less than 4.0 mmol/L.

The sliding scale from Hospital Universiti Sains Malaysia (Hospital USM) is shown in Table 2.2. The BG target range for the Hospital USM ICU is 8.0 – 10.0 mmol/L. The IIT starts with scale 2 when the BG is greater than 10.0 mmol/L, and the BG measurement interval is hourly until the BG is within the target range. The BG

measurement will be four hourly once the BG is within the target range. The scale will be increased by two columns to the right (higher insulin dose) when the current BG is higher than the previous BG. Meanwhile, the scale will be moved to the first left column (lower insulin dose) when the BG readings are between 4.0 – 6.0 mmol/L, and the BG will be monitored hourly.

Based on Table 2.2, some scales have similar insulin doses. For example, when BG is equal to or greater than 10 mmol/L, the insulin doses are similar for scale 2 to scale 4 which is 2.0 U/hr, while scale 5 to scale 7 which is 3.0 U/hr. This may result in no difference in the BG outcomes as the insulin doses administered to the patients are the same.

Table 2.2 Sliding scale obtained from Hospital USM.

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**							

The study found that some scales can be merged and eliminated from this sliding scale which can reduce complexity and prevent confusion among nurses (Zukhi et al., 2020). This study suggested that scale 2 and scale 3 can be merged as the BG outcomes gave similar results for BG < 6.0 mmol/L, 8.0 – 10.0 mmol/L, and > 10.0 mmol/L. The same goes for scale 5 and scale 6 which can be combined. Moreover, this study found that scale 8 gave high insulin doses, but it resulted in an ineffective BG outcome. Thus, scale 8 can be eliminated and reduce the number of scales for simplicity.

Another sliding scale used in Malaysia's ICU is from the University Malaya Medical Centre (UMMC), as shown in Table 2.3 (Ru, 2018). The variation of the sliding scale from UMMC is slightly different from Hospital USM as shown in Table 2.2. The sliding scales are slightly different among centres based on their insulin infusion protocol.

Table 2.3 Sliding scale used in University Malaya Medical Centre

Scale / **Blood glucose (mmol/L)**	**8 unit**	**12 unit**	**16 unit**	**20 unit**
0 – 5	0	0	0	0
5.1 – 10	1	2	4	6
10.0 – 15	2	4	8	12
15.1 – 20	4	6	12	18
20.1 – 25	6	8	16	24
25.1 – 30	8	12	20	30
> 30	**Inform Doctor**			

2.4 Model-based Glycaemic Controller

A model-based glycaemic controller represents an innovative computerised system that assesses patients' insulin sensitivity and metabolic rate, thereby facilitating direct access to their glycaemic levels (Chase et al., 2007; Lonergan et al., 2006). It calculates the S_I value hourly, which is critical for detecting patient dynamics. These are the benefits of the model-based controller that the sliding scale approach does not offer. The initial model created by Chase et al. was a glucose-insulin model, which subsequently progressed into the glucose-insulin model for insulin sensitivity (S_I Test model) and the ICING model (Chase et al., 2007; Lin et al., 2008, 2011).

Many model-based controllers exist for controlling hyperglycaemia including Specialised Relative Insulin Nutrition Tables (SPRINT) and Stochastic TARgeted (STAR) (Chase et al., 2007; Lin et al., 2008). The controller is not limited to suggesting the insulin dosage, but they also include nutrition suggestions which can improve the effectiveness of the IIT. Besides, they can predict the next BG levels which helps the nurses to monitor the ICU patients.

Studies have been done on Malaysian ICU patients by implementing the model-based controller (STAR) for controlling hyperglycaemia events (Abu-Samah et al., 2019; Ahamad et al., 2016). The STAR protocol implemented the BG target range of 4.4 – 8.0 mmol/L was conducted on the Malaysian ICU patients (Ahamad et al., 2016). The findings showed that model-based controllers gave promising results in the Malaysia ICUs by reducing hypoglycaemia episodes compared to sliding scale IIT. Meanwhile, various BG target ranges were investigated in the research conducted by Abu-Samah and colleagues (2019). This study recommended the BG target range of 6.0 – 10.0 mmol/L was more suitable for Malaysian ICU patients, which was able to provide balance performance and safety of the IIT. However, the studies were