ROUTINE INSULIN SLIDING SCALE PROTOCOL VERSUS SOFTWARE DRIVEN ALGORITHM (STAR PROTOCOL) FOR BLOOD GLUCOSE MANAGEMENT OF CRITICALLY ILL PATIENTS IN THE ICU: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

The objective of the study was to evaluate a specifically designed software driven algorithm for the establishment of tight glycaemic control with lesser risks of potentially harmful hypoglycaemia in critically ill patients in the ICU and to compare the results with the routine glucose management protocol i.e. insulin sliding scale, used by the ICU in UMMC. A total of 82 patient's that were admitted to the ICU requiring glucose management protocols were recruited for this study. This was a prospective observational study conducted over a duration of 1 year. Biometric data, feeding and fluid regimens, vital signs and laboratory parameters (haematological, metabolic and biochemical results) were extracted and collected from the patient's hospital ICU records. The data collected was subsequently simulated with the software driven algorithm (STAR protocol) and results were analysed to determine if it was better at maintaining blood glucose levels within set targets of 6-10 mmol/L. Analysis of the entire cohort showed that statistically there was no significant difference between the ISS protocol with the STAR protocol in maintaining glucose control within the set targets of 6-10 mmol/L with a p-value of 0.1556, z-value of -1.42404 and U value of 2928.5. However, the incidence of severe hypoglycaemic events (BG < 2.2 mmol/L) was 0.05% using the ISS arm whereas there was no incidence of hypoglycaemia in the STAR protocol arm. Despite both arms showing similar performance in terms of BG therapy, there is still much room for improvement with the STAR protocol as simulations were made based on Caucasian population pharmacokinetic and pharmacodynamics models. Hence, further work and research in the area of software development and customisation to local epidemiology is required to validate it for use in our clinical practice.

ABSTRAK

Objektif utama kajian ini adalah untuk menentukan keberkesanan suatu algoritma perisian komputer yang dicipta khas (protokol STAR) untuk menguruskan tahap glukosa dalam darah pesakit yang tenat di wad rawatan rapi PPUM dan membandingkannya dengan protokol pengurusan gula darah yang biasa digunakan iaitu protokol Skala Geluncuran Insulin (SGI). Objektif kedua adalah memantau samada ianya dapat mengurangkan insiden hipoglisemia yang berbahaya di kalangan pesakit tersebut. Sejumlah 82 pesakit yang berada di wad rawatan rapi PPUM yang memerlukan pengurusan glukosa darah telah direkrut ke dalam kajian ini. Jangka masa yang telah diambil untuk melengkapkan kajian ini adalah 1 tahun dan adalah berdasarkan pemerhatian prospektif di wad rawatan rapi PPUM sahaja. Data biometrik, regimen pemakanan dan cecair intravena, tanda-tanda hemodinamik serta keputusan makmal (hematologik, metabolik dan biokimia) telah diekstrak dari rekod-rekod pesakit untuk kajian ini. Data-data yang diperolehi kemudiannya disimulasikan oleh perisian computer khas protokol STAR dan keputusannya dibandingkan dengan pengurusan protokol SGI yang biasa. Analisa keseluruhan kohort ini telah menunjukkan bahawa tiada signifikan statistik antara prestasi protokol STAR dengan protokol SGI dari segi menguruskan tahap glukosa darah pesakit dalam lingkungan 6-10 mmol/L dengan nilai P-0.1556, nilai Z-1.42404 dan nilai U-2928.5. Protokol STAR tidak menunjukkan sebarang insiden hipoglisemia yang berbahaya (< 2.2.mmol/L) berbanding dengan protokol SGI iaitu 0.054%. Walaupun tidak menunjukkan perbezaan yang ketara dari segi prestasi, didapati bahawa protocol STAR mempunyai kemampuan untuk diperbaiki lagi disebabkan simulasi yang dibuat adalah berdasarkan model farmakodinamik dan farmakokinetic populasi Kaukasia. Oleh yang demikian, lebih penyelidikan dan penyesuaian protocol STAR kepada epidemiologi tempatan harus dilakukan agar ia dapat diaplikasikan di sini pada masa akan datang.

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my upmost respect and gratitude to Associate Professor Dr. Mohd Shahnaz Hasan, my supervisor and senior consultant of anaesthesiology department PPUM, who had guided me throughout my thesis with his knowledge, expertise and patience.

My gratitude also goes to Dr. Asma Abu Samah, my research collaborator and post doctorate researcher of Institute of Energy and Infrastructure UniTEN, for her help in simulating and analysing the PPUM ICU patient's data using the software driven algorithm (STAR protocol).

Worthy mention also goes to staff, friends and colleagues of PPUM anaesthesia department for their invaluable help and advice in contributing to this thesis work.

A word of thanks to my beloved wife, Phei Fern, for being a pillar of unwavering support from start to completion of my work.

And most of all, to Almighty God through whom all things came and through whom we exist.

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LIST OF SYMBOLS AND ABBREVIATIONS

Term	Definition
APACHE	Acute Physiology and Chronic Health Evaluation
BG	Blood Glucose
CDF	Cumulative Density Frequency
FBC	Full blood count
GCS	Glasgow Coma Scale
GLUT	Glucose Transporter
ICU	Intensive Care Unit
ISS	Insulin Sliding Scale
IQR	InterQuartile Range
MATLAB	4^{th} generation programming language and numerical analysis environment
PPUM	Pusat Perubatan Universiti Malaya
STAR	Stochastic Targeted
SGI	Skala Geluncuran Insulin
UMMC	University Malaya Medical Centre
UniTEN	University Tenaga Nasional
VEGF	Vascular Endothelial Growth Factor

CHAPTER 1: INTRODUCTION

Over the years, a growing body of evidence with regards to tighter glycaemic control and its association with decreased mortality, organ dysfunction, and length of stay in the ICU has caused a paradigm shift in the management of critically ill patients in the intensive care unit.

Pioneering studies such as the DIGAMI study [1] in 1995 brought clinicians to the attention of tight glycaemic control in reducing mortality in patients. Subsequently, two single centre randomized controlled trials (also known as the Leuven Intensive Insulin Therapy trials) by Van den Berghe et al [2], were pivotal in influencing this change as they provided evidence that the normalization of blood glucose by intensive insulin therapy in patients at a surgical and a medical intensive care unit resulted in markedly improved survival for critically ill patients.

A meta-analysis incorporating data from the large multicentre NICE-SUGAR trial in 2009 by Finfer et al [3] confirmed that overall, there was no mortality benefit with tight sugar control (4.5-6.0mmol/L), perhaps with the exception of cardiac surgical ICU patients. Hence, a more relaxed approach to glycaemic control <10mmolL is the general consensus amongst clinicians.

A post hoc analysis of the NICE-SUGAR trial data [4] published in 2012, looking specifically into the prevalence of hypoglycaemia in the critically ill also

concluded that hypoglycaemia and death had a dose-response relationship. Whereby, the strongest correlation was for patients with distributive shock.

Routine glucose management in the UMMC ICU is based on the existing insulin sliding protocol as standard of care. It has been proposed that the generic insulin sliding scale (ISS) protocol may be obsolete in this time and age. The current conventional insulin sliding scale is a 'one size fits all' type of protocol that observes only a single parameter which is the patient's blood glucose measurement as a guide to manage the patient's insulin requirements. This has been deemed too simplistic and may be inadequate to manage the complex physiological differences between each patient. The current overall trend nowadays seems to be gravitating towards the introduction of computerised closed loop automated systems equipped with insulin, dextrose and feeding regimens for blood glucose control and the abolishment of human driven protocols. With the advent of sophisticated and intelligent computer software algorithms, glucose management in patients may be further improved. One such example of software driven algorithm is the STAR protocol adopted in this study. It can be tailored to the patient by encompassing analysis of biometric, hemodynamic, biochemistry and metabolic parameters, calculating individual insulin sensitivity, thus recommending feeding and fluid regimens which would result in better maintenance of blood glucose concentrations within target ranges with lesser incidence of disastrous hypoglycaemic events.

This software algorithm has shown early promising results overseas especially in Caucasian subjects through a retrospective analysis by Kent W. Stewart et al [5] in Hungary and New Zealand but has not yet been proven in South East Asian type patients hence its target implementation in Malaysian ICUs have yet to be established. Hence, the main aim of this study is to determine whether the STAR protocol performs better in ICU patients with regards to glycaemic control and in the reduction of hypoglycaemic risk as compared to the conventional ISS. This study may also give us a glimpse into the future of software driven algorithms and its capabilities in the realm of healthcare.

CHAPTER 2: LITERATURE REVIEW

2.1 LITERATURE SEARCH OF COMPUTERISED CLOSED LOOP SYSTEMS USED IN CLINICAL PRACTICE FOR GLYCAEMIC CONTROL

A general literature search showed that there have been several studies related to this issue comparing routine insulin sliding scale protocols with various software algorithms e.g.:

i. Safety, efficacy and clinical generalization of the STAR protocol; a retrospective analysis by Kent W.Stewart et al [5]

ii. Multicentric, Randomized, Controlled Trial to Evaluate Blood Glucose Control by the Model Predictive Control Algorithm Versus Routine Glucose Management Protocols in Intensive Care Unit Patients by Johannes Plank et al[6]

iii. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multi-center randomized controlled clinical trial by Jasperina Dubois, et al [7]

The abovementioned studies showed better outcome overall with computerised algorithms for glucose control as compared to generic insulin sliding scale protocols used to manage hyperglycaemia of critically ill patients in the ICU setting.

The STAR (**S**tochastic **TAR**geted) protocol utilized in this study is a computerised decision support system for glycaemic control in the intensive care unit co-jointly developed by University of Canterbury New Zealand and UniTEN. It has the

ability to adapt to a patient's physiological condition, personalizing insulin treatment according to their needs by accurately calculating individual insulin sensitivity, predict possible changes in insulin sensitivity and probably prevent hypoglycaemic risks to which conventional insulin sliding scale protocols may fail to do so as effectively.

2.2 PATHOPHYSIOLOGY OF HYPERGLYCAEMIA IN CRITICAL ILLNESS

2.2.1 INCREASED MORTALITY

In one retrospective cohort [8], hyperglycaemia increased incidence of death by 18.3 times and 2.7 times in those with known diabetes. These findings have also been replicated by others [9] who looked specifically at the ICU population.

2.2.2 HYPERGLYCAEMIA AS A KNOWN NEGATIVE PROGNOSTIC INDICATOR

Hyperglycaemia is a known negative prognostic indicator in several patient groups:

i. Trauma [10]
ii. Severe head injury [11]
iii. Subarachnoid haemorrhage [12]
iv. Myocardial infarction [13]
v. Sepsis [14]
vi. Stroke [15]

2.2.3 INCREASED SUSCEPTIBILITY TO INFECTION

Patients who are septic have a higher tendency to develop wound infections and they also have poor wound healing especially after surgery. Inhibition of neutrophil phagocytic activity and oxidative burst due to hyperglycaemia can also disarm the immune system, making it vulnerable even to opportunistic infections.

2.2.4 PRO-INFLAMMATORY EFFECTS

Glucose is a potent pro-inflammatory mediator. Insulin on the other hand has anti-inflammatory effects.

Figure 1: Pathophysiology of hyperglycaemia in critical illness [16]

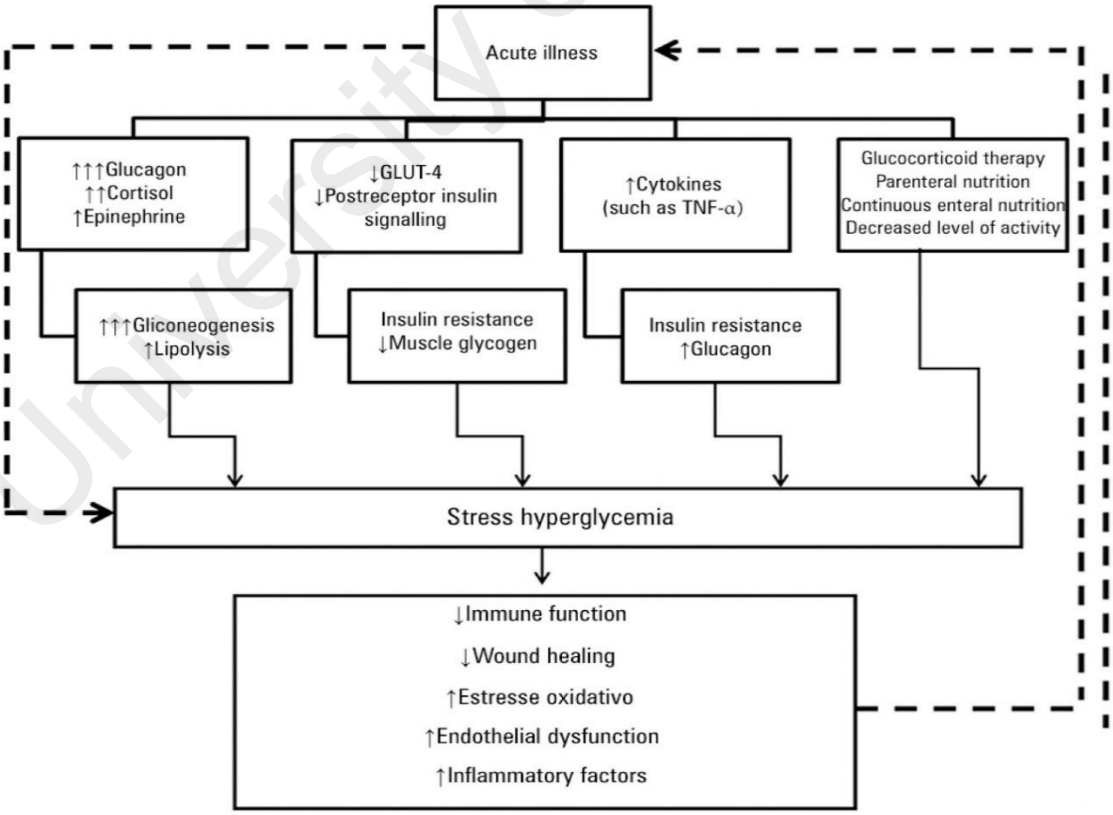
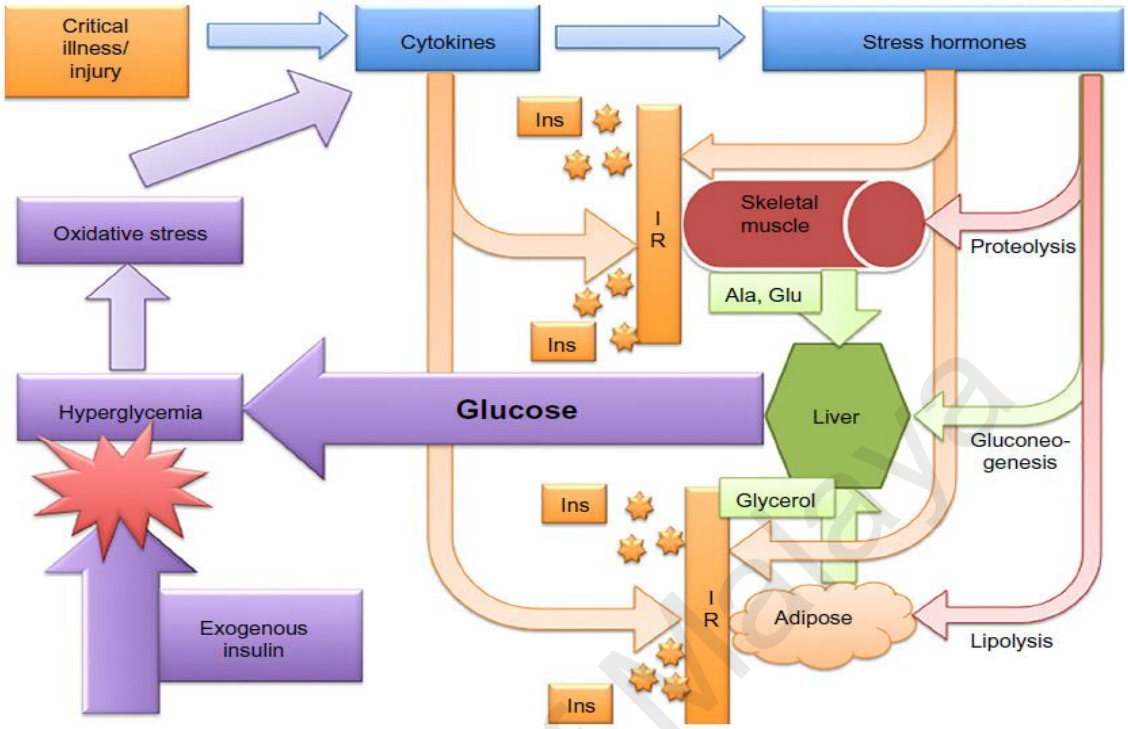


Figure 2: Insulin signalling following acute stress [17]



SURGICAL INFECTIONS, Volume 12, 2011, pp. 405–418, published by Mary Ann Liebert, Inc., New Rochelle, NY, USA.

2.2.5 NEUROENDOCRINE RESPONSE AND METABOLIC EFFECTS

Multiple hormones are released in response to severe stress which activates the neuroendocrine system to release cortisol, norepinephrine, epinephrine, glucagon, and growth hormone [17]. This contributes to systemic inflammation and increased hepatic gluconeogenesis. In acute stress situations, moderate hyperglycaemia may be protective to ensure an adequate glucose supply for the immune system and the brain. [18][19] Increased insulin secretion in response to stress by the pancreas coupled by upregulation of the GLUT transporters, [18] allow for rapid intracellular glucose utilization.

Hypoxia-inducible factors respond to stress-induced hypoxia, upregulate GLUT expression, erythropoietin, and VEGF, and shift away from aerobic to anaerobic metabolism. [17] In the setting of sepsis, glycogen synthesis is inhibited; as a result, a large supply of glucose is available for cellular uptake, largely by the immune cells combating the systemic infection. Although hyperglycaemia provides glucose for immune cells, it also reduces the effectiveness of monocytes, macrophages, and neutrophils via the inhibition of cytokine secretion and myeloperoxidase activity [20]. As in hypoxia, metabolism is shifted toward anaerobic modalities.

Frequently in critically ill patients, insulin resistance is increased over a period of days to weeks; changes in hyperglycaemia and insulin resistance may be indicative of impending infection [21]. Changes in gene expression that occur as a result of changes in hormone levels and the activation of cytokines may result in long-term changes in glucose metabolism [22][23].

CHAPTER 3: STUDY OVERVIEW

3.1 STUDY OBJECTIVES

The primary objective is to determine whether the STAR protocol performs better at maintaining blood glucose within a set targeted range (6-10mmol/L) versus the insulin sliding scale protocol in the ICU setting. The secondary objective is to determine the incidence of severe hypoglycaemic events (<2.2mmol/L) during implementation between the abovementioned protocols.

3.2 STUDY DESIGN

This study is a prospective observational study of patients that were admitted to the UMMC ICU. A total of 82 ICU patients were recruited and followed up during their entire duration of stay in the ICU.

CHAPTER 4: METHODOLOGY

4.1 ETHICAL COMMITTEE APPROVAL

The research was approved by University Malaya Medical Centre Ethical Committee on January 2018. MECID.No: 20171115754. The ethical committee waived the requirement for written informed consent from participants of the study. The first data collection was started on 1st March 2018 and last data collection was on 30th October 2018.

4.2 STUDY POPULATION

Patients in the ICU often develop a condition known as stress induced hyperglycaemia in which blood glucose levels are elevated even without prior history of diabetes. To represent a heterogenous adult population, patients who were critically ill and admitted to the ICU requiring blood glucose control therapy were randomly recruited for this study.

4.2.1 INCLUSION CRITERIA

All patients admitted to the UMMC ICU with an expected stay of at least 24 hours and already receiving or potentially needing insulin for blood glucose control were screened.

4.2.2 EXCLUSION CRITERIA

Criteria for exclusion include:

i. Not critically ill (monitoring only, not requiring vital organ support),

ii. Moribund on admission,

iii. Patients younger than 18 years of age,

iv. Pregnant or breast feeding,

4.3 RESEARCH PROCEDURES

Patients that were admitted to the ICU requiring glycaemic control therapy were screened for exclusion criteria and those that were eligible were recruited and followed up daily until their discharge from the ICU. Data was extracted from the patient's electronic medical records which included:

i. Biometric information – ethnicity, gender, age, weight, height, body mass index

ii. Comorbidities

iii. Hemodynamic parameters – blood pressure, heart rate, oxygen saturations, respiratory rate, GCS

iv. Blood glucose measurements

v. Feeding and fluid regimes – enteral and parenteral, input/output charts

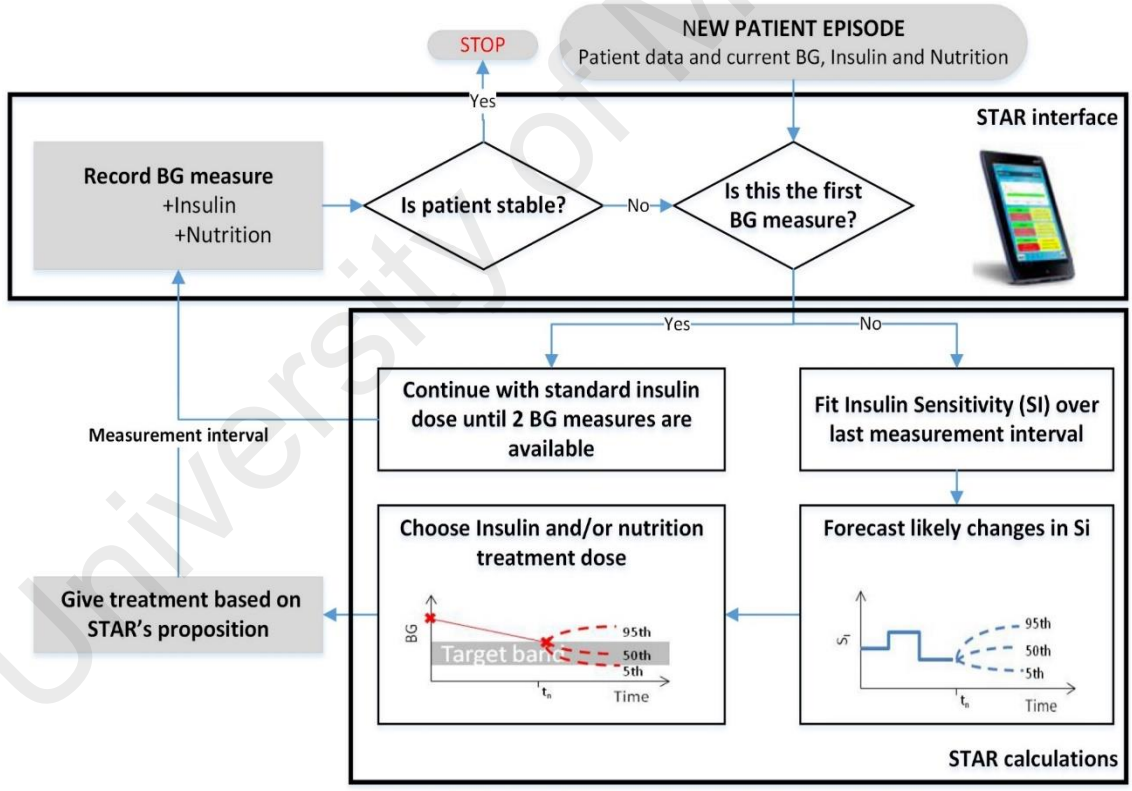
vi. Haematological – FBC, coagulation profiles

vii. Metabolic – blood pH, bicarbonate, base excess, Lactate

viii. Biochemical – Electrolytes, kidney and liver function tests

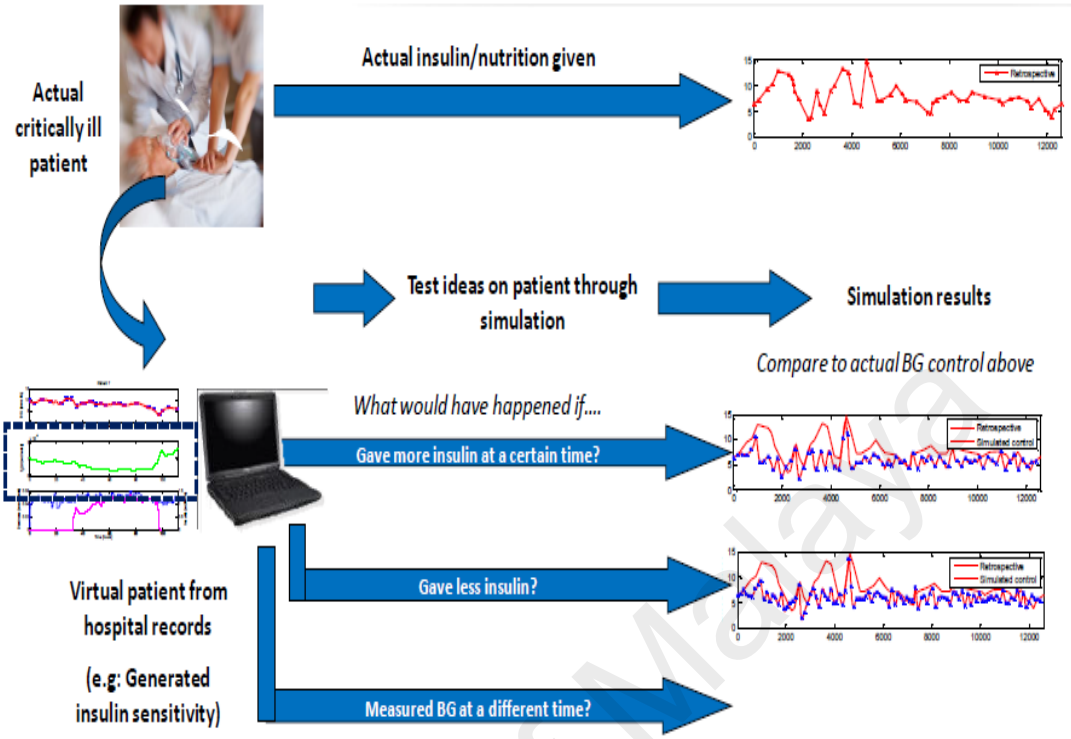
Furthermore, APACHE II scores for each recruited patient were also calculated. The raw data collected was then converted into Microsoft Excel format and subsequently passed on to the collaborators at UniTEN who made simulations from the data using STAR protocol and predictive data was then generated. Eventually both actual insulin sliding scale protocol data and simulated STAR protocol data were analysed and compared.

Figure 3: Workflow of the STAR protocol



STAR protocol is able to implement the glucose–insulin model on any tablet computer with the capability to identify insulin sensitivity, allow forward prediction of interventions to optimize treatments, reduce risk of hypoglycaemia and individualize care.

Figure 4: Virtual analysis and simulation by the STAR protocol



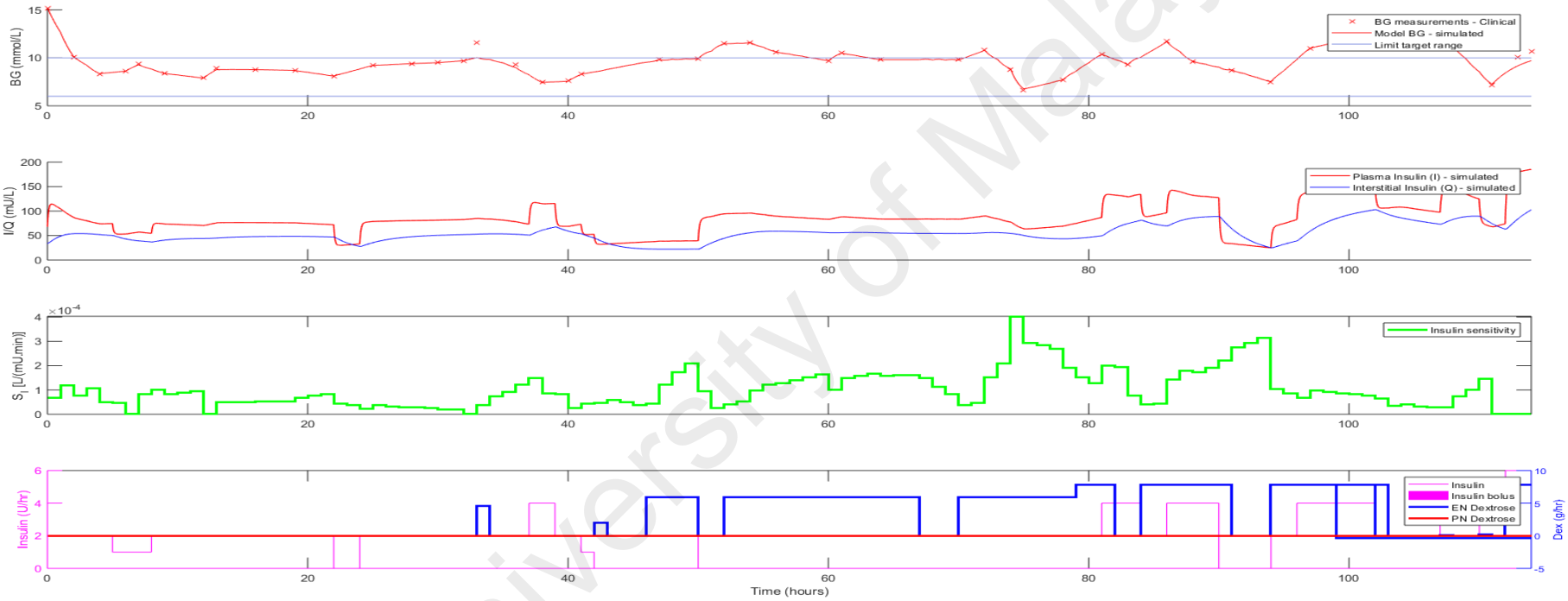
This software driven algorithm also has the capability to generate simulations of virtual patients from actual patient data. Thus, allowing us to test different ideas and include various parameters for simulation to improve glycaemic control.

Figure 5: **Generic insulin sliding scale table used in the UMMC ICU**

SCALE	8 UNIT	12 UNIT	16 UNIT	20 UNIT
0-5	0	0	0	0
5.1-10	1	2	4	6
10.1-15	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 DR	INFORM DR	INFORM DR	INFORM DR

Figure 5 is an example of ISS protocol adopted in many of the Malaysian ICUs with slight inter-hospital variations but generally it's a "one size fits all" type of system and does not take into account many other important parameters to achieve better glycaemic control. Being rather rudimentary, it is unable to explicitly calculate insulin sensitivity, or forward-predict the outcomes of interventions.

Figure 6*:* Example of per-patient BG profile generated from UMMC patient.



The green insulin sensitivity profile is created and acts as a virtual patient to run simulation on STAR control

Figure 7: Schematic presentation of calculation of insulin sensitivity using STAR protocol.

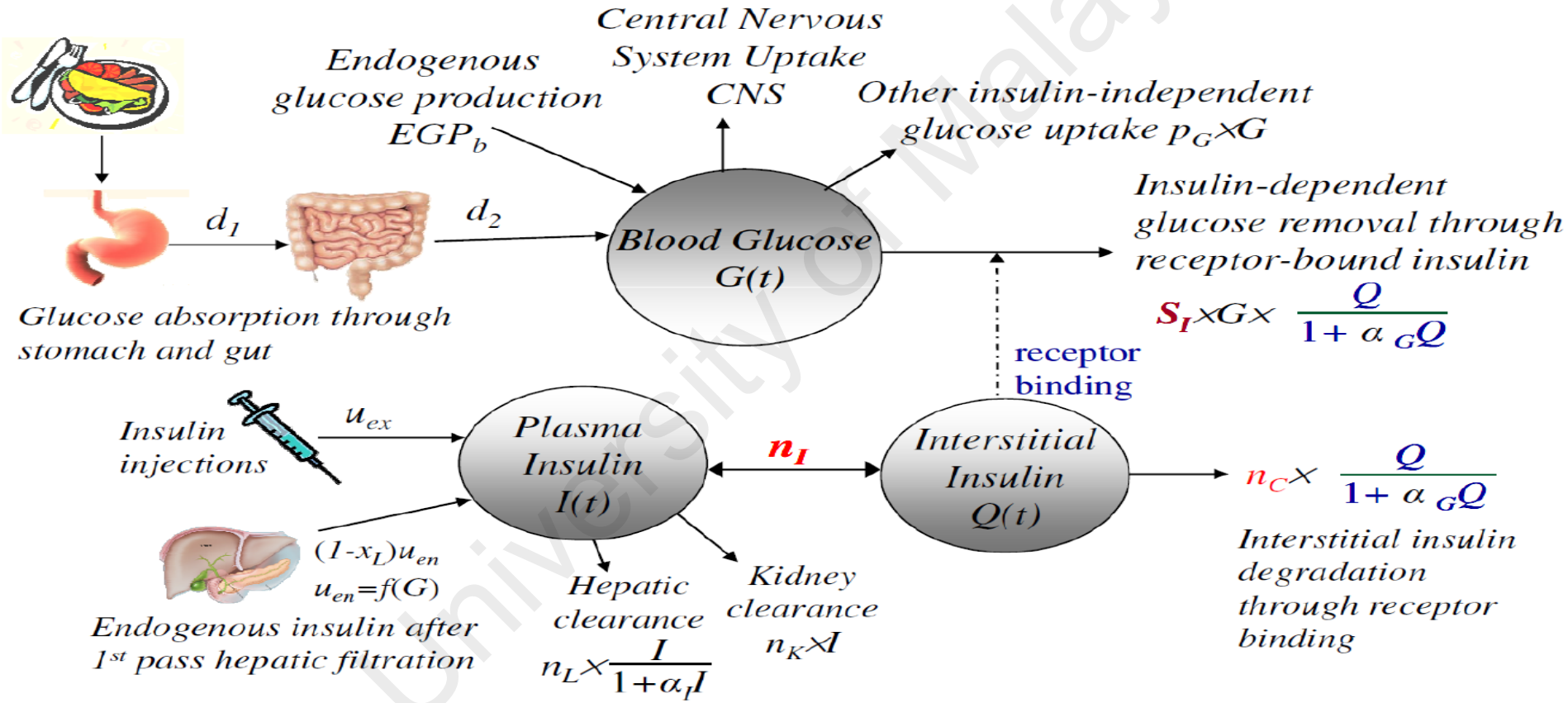


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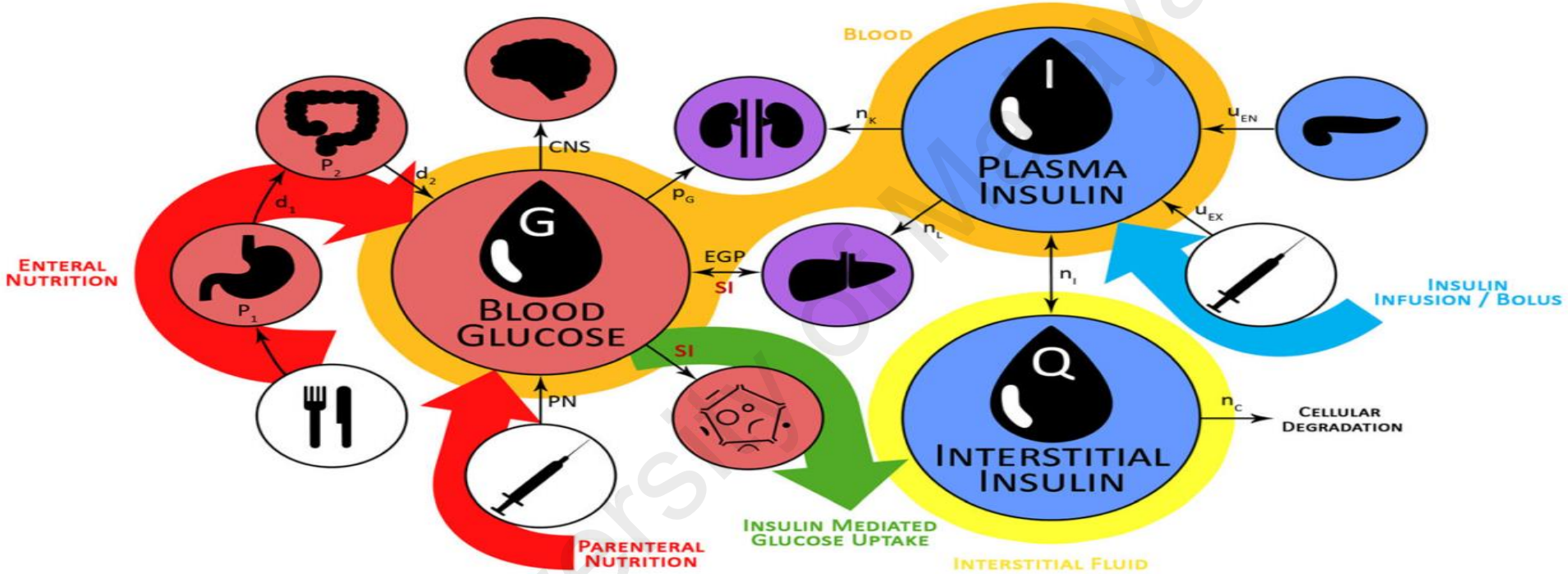
Figure 8: Schematic presentation of pharmacokinetic and pharmacodynamic models used by STAR protocol to predict insulin sensitivity.



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STAR protocol utilizes proprietary pharmacodynamic and pharmacokinetic models and algorithms to calculate specific insulin sensitivity for every patient it encounters taking into consideration various routes of nutrition intake, insulin administration, body compartments, organ and cellular metabolism.

4.4 DATA ANALYSIS

Part 1: Data analysis involved analysis of actual data collected from electronic medical records of the patient and simulated data generated from the STAR protocol software algorithm.

Part 2: Statistical analysis was performed using MATLAB Version R2018A. A comparison of both actual and simulated data was performed looking at which protocol was better in managing blood glucose levels and also the incidence of hypoglycaemic events.

4.5 RESEARCH WRITE UP AND REPORT

Armed with the results of the final analysis from the robust data. A discussion between me, my supervisor (Prof Shahnaz) and collaborators at UniTEN regarding the results were made. Final conclusions were derived and subsequently the research write up was commenced and completed.

CHAPTER 5: RESULTS

Table 1: ISS PROTOCOL DATA

CASE	UMMC CONTROL
Num episodes:	82
Total hours:	9936
Num BG measurements:	3734
Raw measurement outcomes:	
BG median [IQR] (mmol/L):	9.30 [7.80 - 11.20]
BG mean (geometric) (mmol/L):	9.316
BG StDev (geometric) (mmol/L):	1.338
% BG within 4.0 - 10.0 mmol/L:	60.900
% BG within 4.4 - 8.0 mmol/L:	28.281
% BG within 6.0 - 10.0 mmol/L:	**55.463**
% BG > 8.0 mmol/L:	70.996
% BG > 10.0 mmol/L:	**38.698**
% BG < 4.4 mmol/L:	0.723
% BG < 4.0 mmol/L:	0.402
% BG < 3.0 mmol/L:	0.080
% BG < 2.2 mmol/L:	0.054
Num patients < 2.2 mmol/L:	**1**
Median time to 10.0 mmol/L (hour)	3.0 [0.0 - 10.0]
Median insulin rate [IQR] (U/hr):	1.0 [0.0 - 2.0]
Median glucose rate [IQR] (g/hour):	0.7 [0.0 - 5.9]
Median glucose rate [IQR] (% goal):	0.0% [0.0% - 0.0%]
Hourly resampled stats:	
Hours of control:	10018
BG median [IQR] (mmol/L)	**9.1**
BG mean (geometric) (mmol/L):	9.202
BG StDev (geometric) (mmol/L):	1.289
% BG within 4.0 - 10.0 mmol/L:	**64.634**
% BG within 4.4 - 8.0 mmol/L:	27.211
% BG within 6.0 - 10.0 mmol/L:	**60.661**
% BG > 8.0 mmol/L:	72.410
% BG > 10.0 mmol/L:	**35.187**
% BG < 4.4 mmol/L:	0.379
% BG < 4.0 mmol/L:	0.180
% BG < 3.0 mmol/L:	0.030
% BG < 2.2 mmol/L:	0.020
Num patients < 2.2 mmol/L:	**1**
Num incidences< 2.2 mmol/L:	**2**

TABLE 2 Simulation Data With STAR Protocol

Num episodes:	82
Total hours:	9885
Num BG measurements:	6650
Raw measurement outcomes:	
BG median [IQR] (mmol/L):	9.12 [7.51 - 10.70]
BG mean (geometric) (mmol/L):	8.941
BG StDev (geometric) (mmol/L):	1.291
% BG within 4.0 - 10.0 mmol/L:	62.256
% BG within 4.4 - 8.0 mmol/L:	32.015
% BG within 6.0 - 10.0 mmol/L:	56.677
% BG > 8.0 mmol/L:	67.218
% BG > 10.0 mmol/L:	37.263
% BG < 4.4 mmol/L:	0.767
% BG < 4.0 mmol/L:	0.481
% BG < 3.0 mmol/L:	0.045
% BG < 2.2 mmol/L:	0
Num patients < 2.2 mmol/L:	0
Median insulin rate [IQR] (U/hr):	2.0 [1.0 - 4.0]
Median glucose rate [IQR] (g/hour):	2.2 [0.0 - 6.5]
Median glucose rate [IQR] (% goal):	33.5% [0.0% - 99.3%]
Hourly resampled stats:	**STAR 6-10.0 mmol/L**
Hours of control:	9967
BG median [IQR] (mmol/L)	8.6
BG mean (geometric) (mmol/L):	8.666
BG StDev (geometric) (mmol/L):	1.253
% BG within 4.0 - 10.0 mmol/L:	73.081
% BG within 4.4 - 8.0 mmol/L:	36.701
% BG within 6.0 - 10.0 mmol/L:	69.168
% BG > 8.0 mmol/L:	62.777
% BG > 10.0 mmol/L:	26.598
% BG < 4.4 mmol/L:	0.522
% BG < 4.0 mmol/L:	0.321
% BG < 3.0 mmol/L:	0.030
% BG < 2.2 mmol/L:	0.000
Num patients < 2.2 mmol/L:	0
Num incidences< 2.2 mmol/L:	0

INTERPRETATION OF TABLE 1 AND 2:

The number of BG measurements was significantly higher for the STAR arm (6650) showing almost double the numbers required in the ISS arm (3734).

The number of incidences of hypoglycaemia is 2 with the ISS protocol while the STAR arm did not register incidences of hypoglycaemia.

Percentage of BG in the targeted 6-10 mmol/L band was only 60% for ISS protocol while percentage of BG in the same band was slightly better with STAR protocol showing 69%

Median insulin rate for ISS is 1.0 U/hr while median insulin rate for STAR is 2.0 U/hr meaning that insulin requirement was doubled. Median glucose rate (g/hr) was higher in the STAR protocol compared to ISS protocol showing 2.2 and 0.7 respectively which is reflected in the higher insulin rate requirements.

Median glucose rate to achieve the targeted goal of 6-10mmol/L was significantly higher in STAR protocol.

STAR protocol hourly sampled rates showed lower percentage of hyperglycaemia that is 26% compared to ISS with 35%.

TABLE 3: Significance Test Between Real Data And Simulated Data

U-Value (Mann-Whitney test)	2928.5
Significance Z-test with UMMC control	-1.42404
Significance P-test with UMMC control	0.1556
Significance	No

INTERPRETATION OF TABLE 3:

Alternative hypothesis: STAR protocol performed better at glycaemic control compared to ISS protocol.

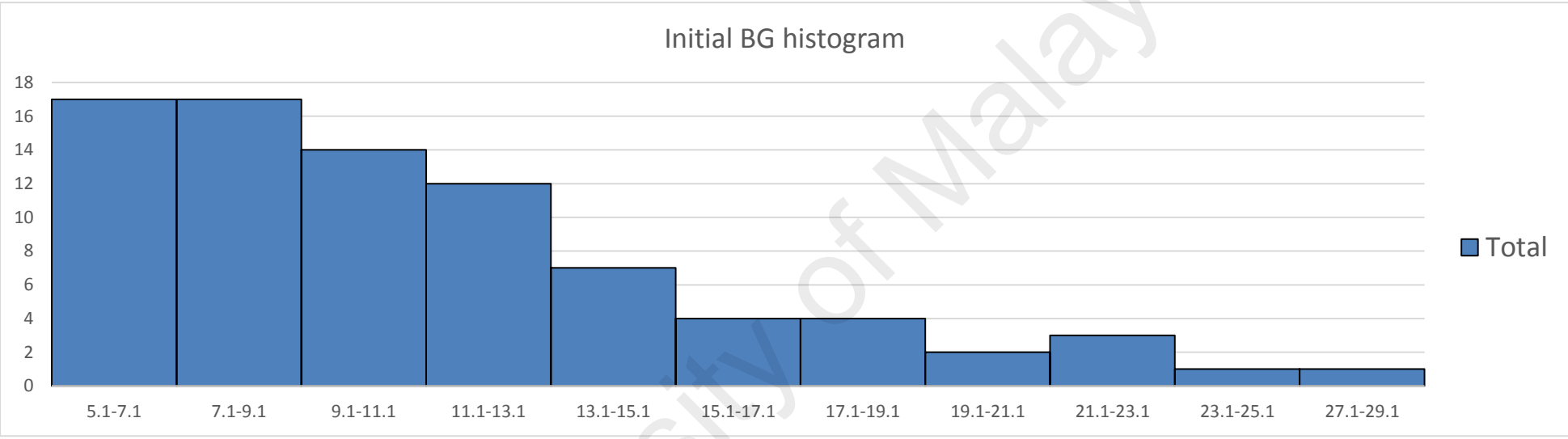
Null hypothesis: STAR protocol does not perform better at glycaemic control compared to ISS protocol.

The U-value in this context represents the number of times observations in one data set precede observations in the other data set in ranking.

The Z-test is a statistical test for which the distribution of the test statistic under the null hypothesis can be approximated by a normal distribution.

P value of 0.1556 (>0.05) with a Z-score of -1.424 and U value of 2928.5 indicates that it fails to reject the null hypothesis. Hence, it also concludes that there was no statistical significance between the real data and simulated data.

TABLE 4: The number of total patients with each initial BG interval.



In this data sample showing patients (actual data) with initial BG measurements on admission to the ICU, it is interesting to note that a large number of patients (approx. 54) recorded near normal blood glucose measurements of ranges from 5.1-11.1 on presentation whereas those that registered BG measurements of > 11.1 (which were deemed hyperglycaemic) were approximately 28 patients.

Figure 9: Per patient CDFs of BG concentration based on ISS

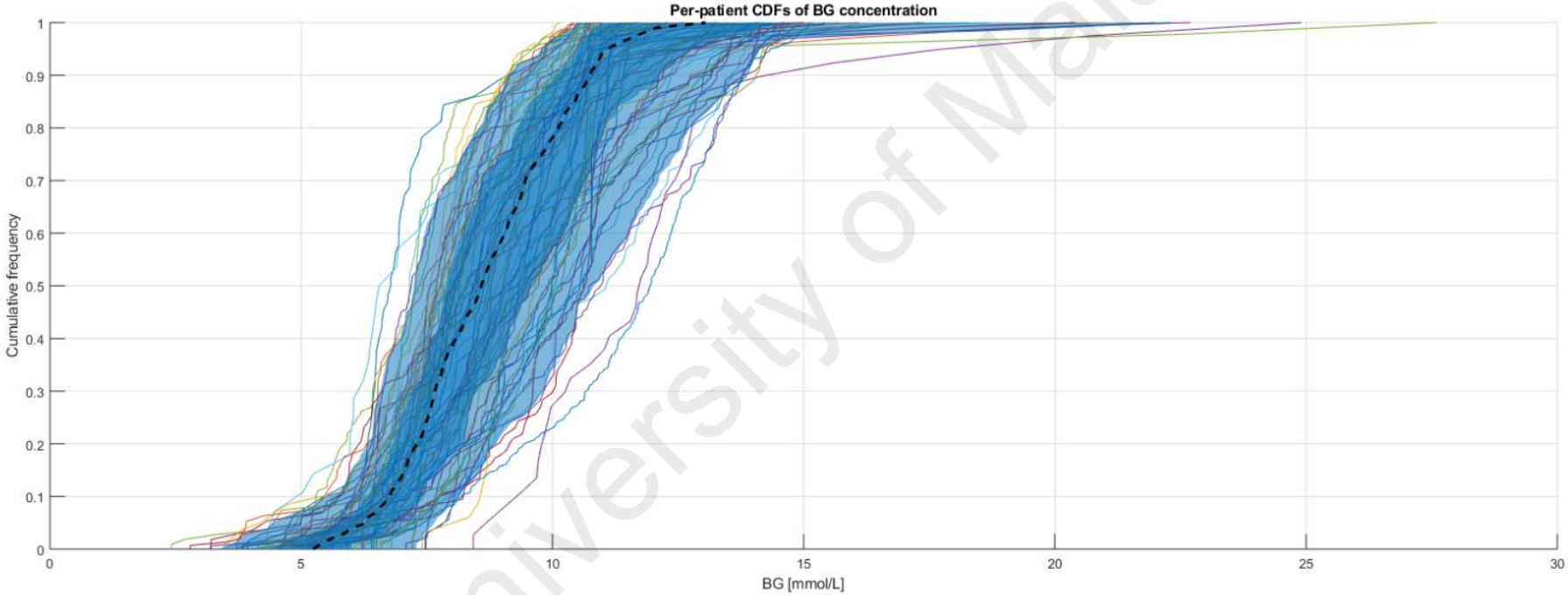
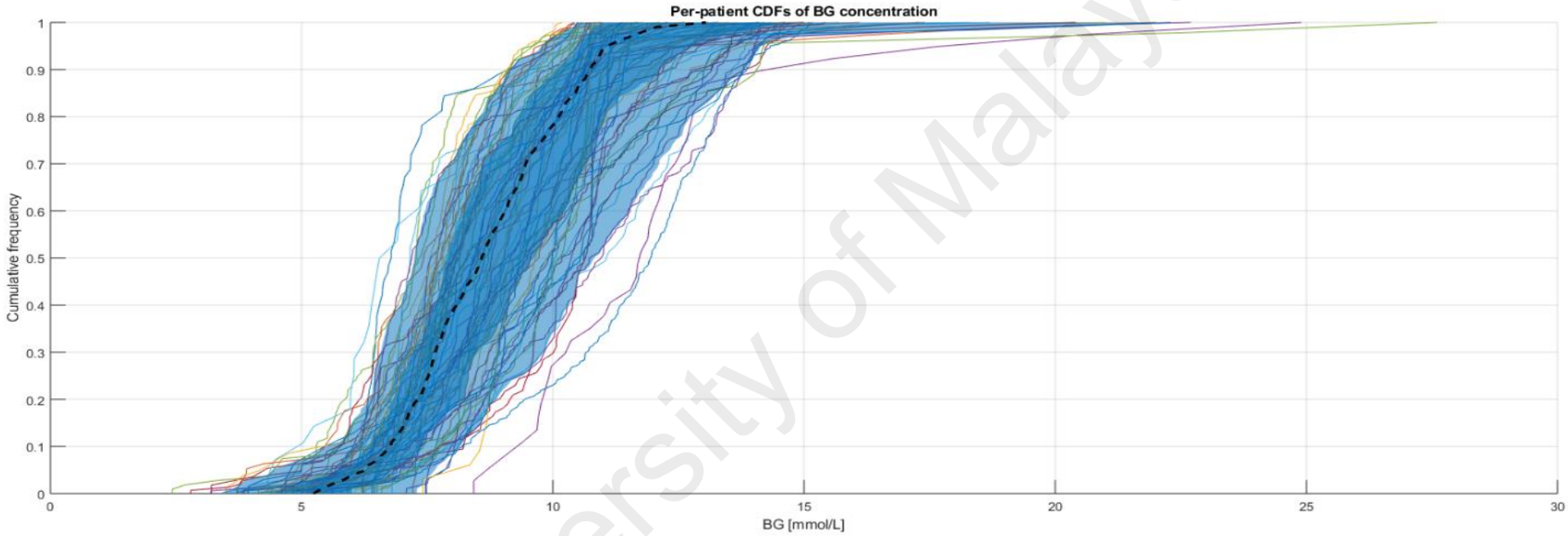
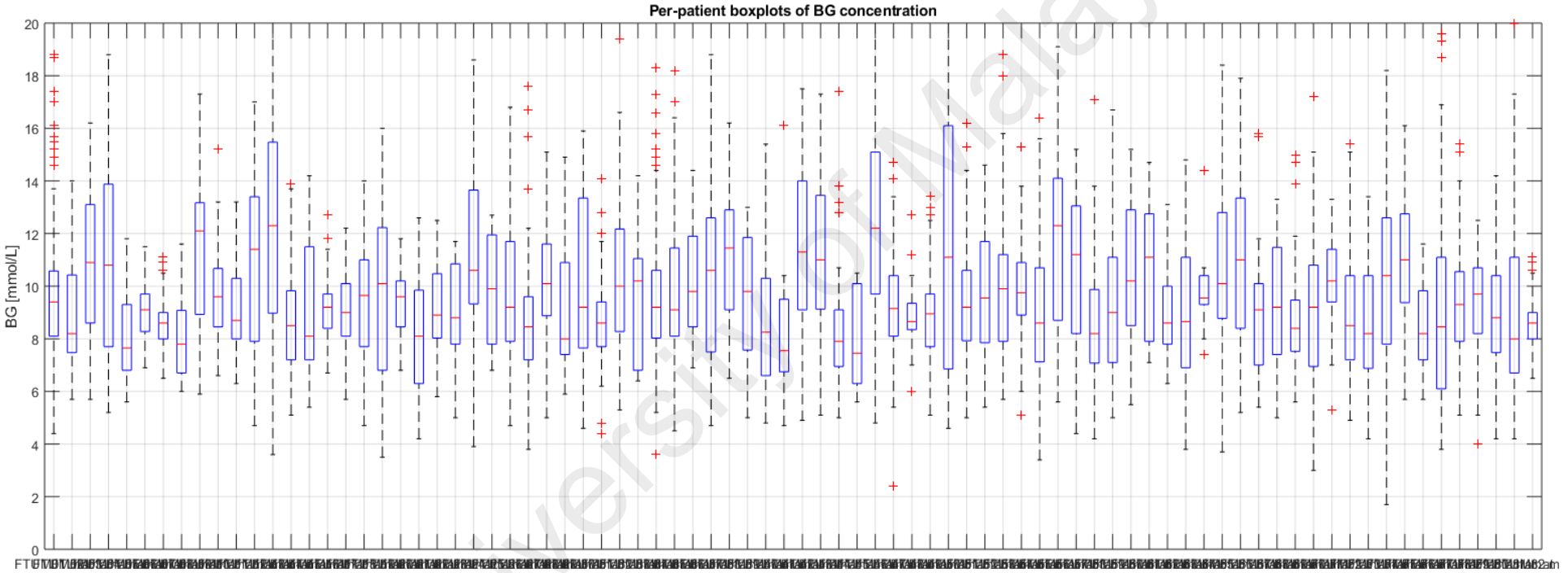


Figure 10: Per patient CDFs of BG concentration based on STAR protocol



Both Figure 9 and 10 shows the cumulative density plots per patient in the ISS and STAR protocols respectively. Comparison of both plots indicate that BG distributions were almost identical with BG standard deviations (geometric) 1.33 mmol/L and mean (geometric) 9.3 mmol/L for ISS; BG standard deviations (geometric) of 1.29 mmol/L and mean (geometric) 8.9mmol/L for STAR. Thus, this gives evidence that the performances of both protocols were generally rather similar in terms of glucose control.

Figure 11: Per patient boxplots of BG concentration based on ISS



The red '+' in the box-plots indicate the outlier numbers outside the median and interquartile ranges (IQR) of the BG measurements for each patient (total 82)

Figure 12: BG Boxplot For UMMC Virtual Patients And Simulated With STAR Protocol

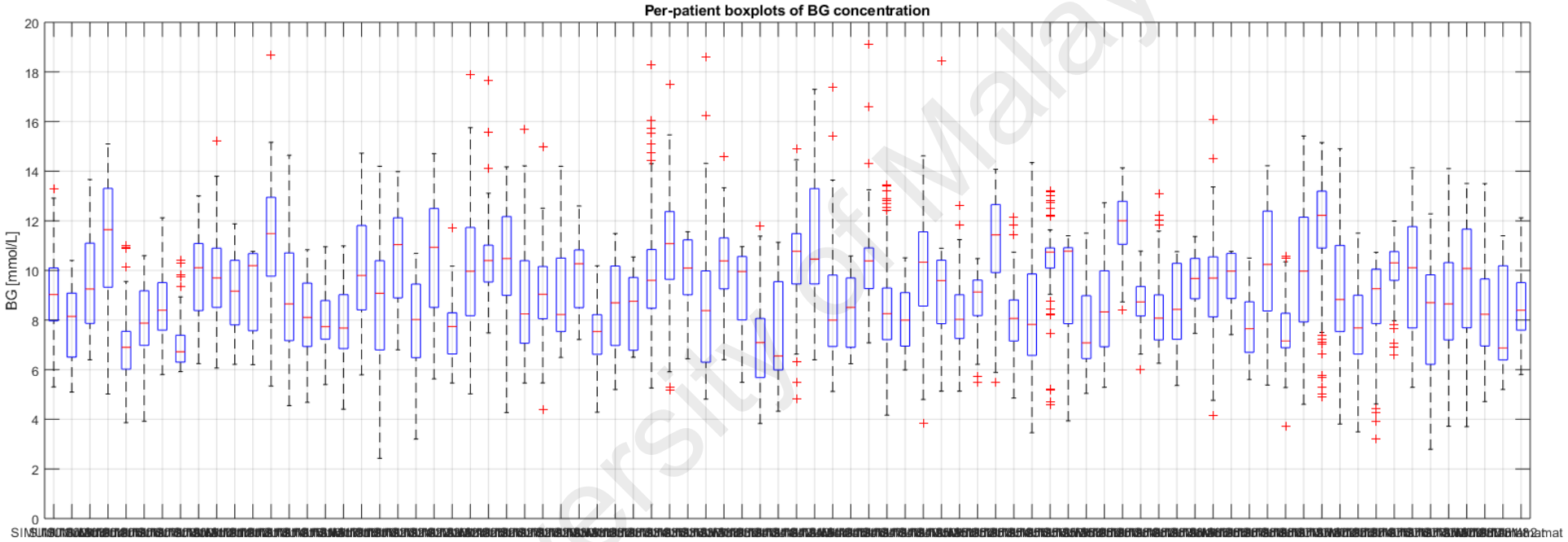


Figure 11 shows a greater variability with wider and more outlier measurements recorded as compared to the STAR protocol boxplot (Figure 12). This translates to less 'tight' glucose controls in the ISS protocol group and greater deviation from the IQR.

CHAPTER 6: DISCUSSION

6.1 PERFORMANCE AND STATISTICAL SIGNIFICANCE

Poor glycaemic control can lead to devastating outcomes for critically ill patients in the ICU. High blood sugar levels are associated with increased mortality, length of hospital stay, infection rates, mechanical ventilation days, adverse cardiac events, heart failure, critical illness polyneuropathy and/or multi-organ failure. Thus, there is a need to improve on current blood glucose management therapy methods. In this technological age, there has been a push towards the development of software driven algorithm closed loop systems with the hopes of improving blood glucose management therapy in patients. This study was to ascertain whether a particular software driven algorithm i.e. STAR protocol performed better at glycaemic control as compared to the conventional insulin sliding scale protocol used in the UMMC ICU. Analysis of the entire cohort showed that there was no significant statistical difference between both the protocols in terms of controlling blood glucose levels between set targets of 6-10mmol/L. The ISS arm resulted in over 60% of time per episode in the blood glucose (BG) band of 6-10mmol/L compared to the STAR protocol arm showing only slightly better performance of 69% of time per episode with a p-value of 0.1556, z-value of -1.42404 and U value of 2928.5. The results also showed that the STAR protocol outperformed the ISS protocol in terms of lesser percentage of time per episode of hyperglycaemia (BG>10mmol/L) i.e. 26% with STAR protocol as compared to 35%

with ISS. However, the incidence of severe hypoglycaemic events (BG < 2.2 mmol/l) was 0.05% using the ISS arm whereas there was no incidence of hypoglycaemia in the STAR protocol arm. Graphical presentation in Figures 9 and 10 also indicate clearly that the cumulative distribution frequencies for both protocols were rather identical hence reinforcing the fact that performances for both protocols were not significantly different. That being said, the Figures 11 and 12 grossly showed greater variability and more outlier measurements for the ISS protocol thus indicating that the STAR protocol may have been slightly better in tighter glycaemic control but not significant enough statistically.

The above results were not congruent with the research findings by Kevin W. Stewart et al [4], which was based on a dual centre retrospective analysis of STAR protocol data. In that study, he was able to demonstrate a higher nutrition and equally safe, effective blood glucose control of more than 90% of time per episodes within in the BG band of 6-10mmol/L for all the days of patient stay, while lowering the number of measurements and interventions required. This is probably due to the fact that the software algorithm was based on pharmacokinetic and pharmacodynamic models derived from Caucasian populations. Hence, genetic makeup, diet, cultural, physiological, and geographical differences might have to be taken into account into tailoring this software to suit the needs of the local population.

6.2 STUDY LIMITATIONS

There were some limitations to the study that might have influenced the results of the analysis which includes:

Firstly, the actual data collected was simulated with STAR protocol and then compared. Being simulated data, it can only give us a rough idea on how well the STAR protocol is able to perform in the real world setting. Hence accuracy of the simulated data may not represent actual performance. Future studies can be conducted to provide direct implementation of the STAR protocol on actual patients and comparing them with the patients who were on conventional insulin sliding scale.

Secondly, the study might not have adequate sample size. This is due to time limitation and financial constraints.

Thirdly, follow up of the patient in the wards after discharge from ICU may further provide valuable information in terms of looking at the impact of tight glycaemic control and hypoglycaemic events post ICU care.

Lastly, there may have been lapses in charting of data parameters by healthcare staff into the electronic medical records due to their busy work schedule which might have influenced the results of the eventual analysis.

6.3 COST EFFECTIVENESS

As can be seen in Tables 1 and 2 in the results section. It is noted that sampling frequencies for the STAR protocol (total number of BG measurements) were nearly doubled of ISS protocol which numbered 6650 to 3734 respectively. This translates to double the amount of glucose strips required for blood sampling which would inevitably drive up cost not to mention increased workload for healthcare staff. In view that there were no significant differences in outcomes from both STAR and ISS arms from the statistical analysis above, the cost to benefit ratio of the STAR protocol is still far off from the level to provide the highest "value for money". Proprietary issues may also have to be looked into if the STAR protocol is being implemented as this may mean increased financial expenditure for healthcare facilities and patients.

CHAPTER 7: CONCLUSION

Although initial analysis of the data from this study showed that there was no significant difference between conventional ISS protocol and STAR protocol in terms of blood glucose management therapy in the critically ill, it is still premature to conclude that software driven algorithms are inferior as there can still be ample room for improvement. As can be seen in studies conducted in Caucasian populations, these systems have shown promising results in recent years. The advantage of computerised software systems is that they have the ability to adapt and are constantly being improved on and fine-tuned to meet the needs of the Malaysian population model exclusively. Hence, further work and research is needed to validate these software driven closed loop systems in clinical practice. Perhaps implementation of the STAR protocol to actual ICU patients in the near future may provide us a better understanding on how to utilise and maximise the potential of these systems to benefit our patients and maybe someday do away with the generic insulin sliding scale protocol. It is hoped that one day newer and improved software systems would not only be able to reduce the workload of healthcare staff but also be an ideal and cost effective tool for the caregiver in terms of excellent glycaemic control. This then would also translate to reduced morbidity and mortality for the patients which is the ultimate goal of every physician.

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