Investigation on Different Types of Blood Glucose Control System

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ABSTRACT

Basically it is a case study on proposed blood glucose protocols. Among the protocols been implemented in Intensive Care Unit or critically ill patients were been studied and the outcome of this project is to propose the suitable blood glucose protocol for critically ill patients in Malaysia. Two main protocols known as HTAA and SPRINT been implement in Hospital Tengku Ampuan Afzan Malaysia and Christchurch Hospital, New Zealand respectively. Besides of studying whether both protocols are capable to reduce the mortality rate, these two are compared in terms of patients suitability whether they can adapt to the current protocols or not. Next to find out whether both protocols are same in their goal and the significant level of the patient's data obtained from both hospitals (HTAA and Christchurch). In order to find out the patients data is significant or not and the goal of the protocols whether similar, some statistical analysis been carried out solidify the hypothesis statement. This is to ensure the outcome statement of proposing the best protocol between HTAA and SPRINT to critically ill patients in Malaysia.

Keywords: *blood glucose, control, protocols, critically ill patients, analysis*

Introduction

Diabetes mellitus is a kind of disease may give a long term effects to the body [1]. Regardless of races, environmental factors, gender, genetic inheritance, physical conditions and lifestyles are taken in account of leading to diabetes mellitus [2]. Diabetes for a long term may lead to other diseases like kidney malfunction, cardiovascular disease, eye damages, nerve damages, and slow healing wound [3]. Hence, diabetic patients may suffer

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from a lot of diseases after a long term effect. Basically, diabetes mellitus occurs due to destruction of β-cell which is located in the pancreas[4]. β-cell plays an important role in secreting insulin hormone which lowers the blood glucose level [4]. Excluding normal patients, since they are able to control the blood glucose level naturally, some special protocols been introduced to the diabetic patients to monitor and control their blood glucose level from time to time to ensure their safety [5]. Scientific study had proved that extreme blood glucose level may lead to faint or for the worst case may find glucose content in urine [6]. Therefore implementing blood glucose control system protocols is necessary as a precautionary steps and increases alertness among critically-ill patients. In fact, protocols reduce clinical workload and extreme cost. However, every protocol has been adapted to it algorithm which act as a controller. Patient's conditions are considered in every aspect according to the suitability of each protocol. Studies have shown mortality rate can be reduced by controlling the hyper glycaemia to normal level in Intensive Care Unit (ICU). Malaysia Intensive Care Units uses Intensive Insulin Therapy (IIT) as current standard protocol [7]. The expected output of this study is to propose the best protocol for Malaysian patients.

Problem Statement

Manual protocol has been considered unable to control hyperglycemia situation which cause unexpected mortality among critically ill patients. Back in time there is lack of technological development of blood glucose control system protocols [8]. Since there are many advanced protocols been implemented in western country, it is necessary to propose a suitable protocol that can be fully automated in order to prevent hyper glycaemia situation and reduce mortality among critically ill patients. Besides, the proposed protocols can be applicable in labs, clinics or hospitals which reduce the implemented field workload.

Objective

1) To investigate on different types of proposed blood glucose control system.
2) To validate the patients result based on the proposed blood glucose control protocol.
3) To propose the suitable blood glucose control protocol to critically ill patients in Malaysia.

Project Scope

This project targets for Malaysian patients suitability in adapting to proposed blood glucose control protocol. Specifically highlights on protocols, the mathematical model involved among them, targeted patients for each protocol involved. As the result, several statistical analysis method been

chosen to outcome with the statement of the suitable protocol for Malaysian patients.

Methodology

Collaboration has been done with Tengku Ampuan Afzan Hospital (HTAA) and Christchurch Hospital together 91 and 349 ICU patient's data obtained from HTAA and Christchurch respectively. These ICU patient's blood glucose has been monitored every hour in a week, together the particular concentration of insulin been infused on every patients for specified hour in a week. It has been found that HTAA and Christchurch practicing respective blood glucose protocol known as Hospital Tengku Ampuan Afzan (HTAA) protocol and Specialized Relative Insulin and Nutrition Tables (SPRINT) protocol. The aim of this chapter is to find out whether both protocols are similar in their goal or totally different from the goal. Besides to find out the data obtained from both hospitals are significant or not. Therefore, statistical analysis method has been chosen to solidify and outcome with the statement by using Microsoft Excel. The patient's code in HTAA recognize as 'GXXX' while for Christchurch hospital is '5XXX' where 'X' represent the number.

Statistical Analysis

Case study for this project shows that statistical analysis is the satisfactory method to outcome with the best result and clear statement of the most suitable protocol and algorithm for critically ill patients in Malaysia. Out of many analyses, 3 statistical analysis have been chosen listed below:

1) Mann-Whitney U Test.
2) Regression Analysis (Linear Regression).
3) Analysis Of Variance (ANOVA) Table.

Result

Scatter Plot

The patient's data from both hospitals were transferred into Microsoft Excel, the average of blood glucose and insulin infusion for each patient were calculated in Microsoft Excel for 91 patients from HTAA followed by 394 patients from Christchurch. Two graphs have been generated for each hospital patient's data using Microsoft Excel in the form of scatter plot under 95% confidence interval. One is average blood glucose upon patients another is insulin infusion upon patients. The exact values of , 1st quartile (Q_1) and 3rd quartile (Q_3) under 95% confidence interval are not identify since form the plot it is not possible unless of estimation, later the data been generated in 'Descriptive Statistic' together will obtain the grand mean ($\bar{X}$), mode (Mo) and median (Q_2) as well using Analysis Tool pack in Microsoft Excel. The

scatter plot reasons to identify the outliers patients and extract their information besides finding the reasoning of been in such way.

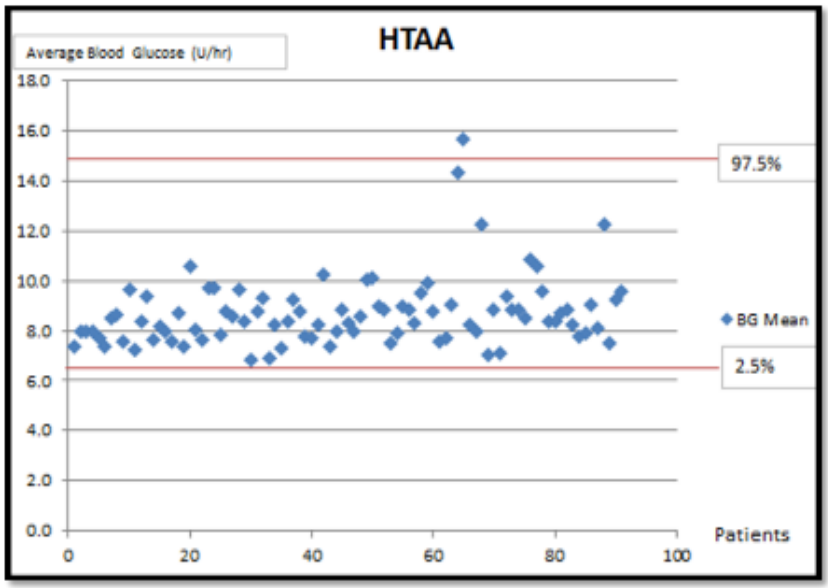

Figure 1: Average Blood Glucose for HTAA

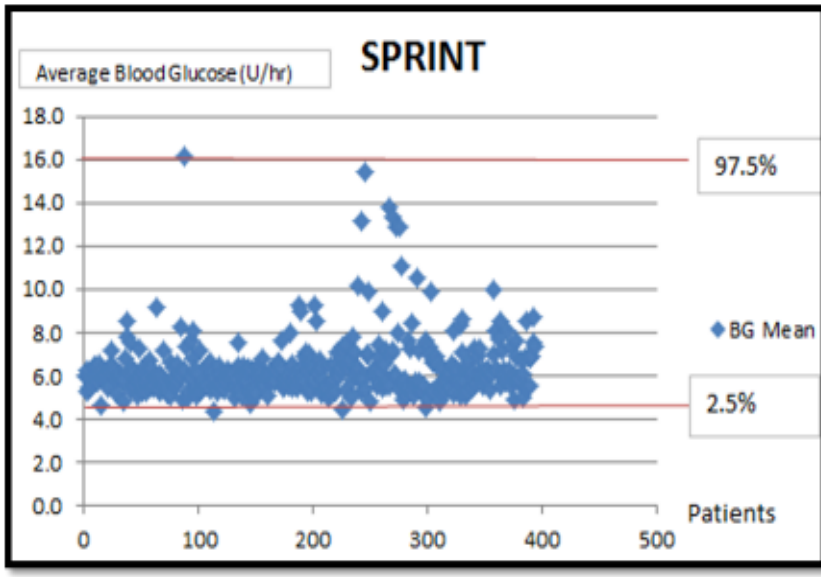

Figure 2**:** Average Blood Glucose for SPRINT

Based on Figure 1, most of the average blood glucose data are within the interval of 97.5% (Q_3) and 2.5% (Q_1) for 95% confidence interval. Out of 91 patients, it is found that 90 patient's average blood glucose data are within the line intervals. Only one patient's data is out of the range and known as an outlier since the data is beyond 97.5% line. Most of the ICU patients might adapt to HTAA protocols based on the scatter plot. Since all 91 patients are from different ages, gender, weight, height and ethnicity (Malay, Chinese, Indian and Foreigner) according to the patients demographic, there is a chance that their average blood glucose been control by HTAA protocol by suitable amount of insulin infusion.

While on Figure 2, most of the average blood glucose data are within the interval of 97.5% (Q_3) and 2.5% (Q_1) for 95% confidence interval. Out of 394 patients, it is found that 392 patient's average blood glucose data are within the line intervals. There are 2 patients data are out of range where one is beyond 97.5 % line while another is below 2.5% line. Since all 394 patients are from different ages, gender, weight, height according to the patients demographic, there is a chance that their average blood glucose been control by SPRINT protocol by suitable amount of insulin infusion. More outliers been found in SPRINT protocol compared to that of HTAA protocol. But, the data significant level is still undefined, with only scatter plot doesn't shown any strong evidence of how significant it is. Therefore, some statistical analysis been carry out to valid the statement.

Table 1: Blood Glucose Analysis (HTAA)

HTAA Protocol Blood Glucose Statistical Analysis	
Mean	8.71
Standard Error	0.15
Median	8.39
Mode	8.26
Standard Deviation	1.41
Sample Variance	1.98
Kurtosis	8.29
Skewness	2.37
Range	8.82
Minimum	6.83
Maximum	15.65
Sum	792.24
Count	91.00
Third Quartile,Q3 (97.5%)	15.36
First Quartile,Q1 (2.5%)	7.12

Table 2: Blood Glucose Analysis (SPRINT)

SPRINT Protocol Blood Glucose Analysis	
Mean	6.34
Standard Error	0.07
Median	6.53
Mode	6.03
Standard Deviation	1.44
Sample Variance	2.07
Kurtosis	15.03
Skewness	3.28
Range	11.84
Minimum	4.35
Maximum	16.19
Sum	2498.39
Count	394
Third Quartile,Q3(97.5%)	16.05
First Quartile,Q1(2.5%)	4.49

Based on Table 1, the grand mean, $\bar{X}$ for the blood glucose is 8.71 U/hour while Q_2 and mode are 8.39 U/hour and 8.26 U/hour respectively. The Q_1 and Q_3 for 95 % confidence interval are 7.12 U/hour and 15.36 U/hr. In terms of measuring the central tendency, this data is in such way mode < median < mean. Hence, the values for 95 % confidence interval are 8.39 U/hour [7.12 U/hour, 15.36 U/hour]. The patient's data which is consider as outlier is extracted from the patients demographic and tabulated for average blood glucose of HTAA protocol as shown below.

Table 3: Outlier Data

Patient Code	Age	Gender	Ethnicity	BMI	Diagnosis	Death
G065	26	Male	Malay	29.3	Leptospirosis	No

Based on Table 3, the patient, G065 suffers from Leptospirosis, is a kind of an infectious bacterial disease transmitted through blood [9]. The patient is facing a blood related illness and needed to be given a high federate, causing to have an extreme average blood glucose level as shown in Figure 4, which is 15.7 U/hour, in addition based on the body mass index, this patient is overweight which is 29.3 considering another factor of having high average blood glucose.

Based on Table 2, the grand mean, $\bar{X}$ for the blood glucose is 6.34 U/hour while Q_2 and Mo are 6.53 U/hour and 6.03 U/hour respectively. Q_1

and Q_3 for 95 % confidence interval are 4.49 U/hour and 16.05 U/hour. In terms of measuring the central tendency, this data is in such way mode < mean < median. Hence, the values for 95 % confidence interval are 6.53 U/hour [4.49 U/hour, 16.05 U/hour]. The patient's data which are consider as outlier are extracted from the patients demographic and tabulated for average blood glucose of SPRINT protocol as shown below.

Table 4**:** Outlier Data

Patient Code	Age	Gender	Diagnosis Code
5087	72	Male	CAH, COL
5113	55	Female	RPLA, SGLBO

Unlike HTAA ICU patients, Christchurch patients are diagnosis with more than 1 disease, the diagnose code obtained from patients demographic and been created in chart form to make it easier to identify patients diagnosis. All the necessary diagnosis codes have been described in table form. Based on Table 4, it has been found patient 5087 is male with an age of 72 considered as twilight age, suffer from hypotension, abnormal low blood pressure and stayed out of hospital. The average blood glucose obtained from the demographic is 16.2 U/hour. Due to imbalanced diet or blood related problems, the average blood glucose might be high. Patient 5113 is a female with an age of 55, suffers from obstruction and aspiration, due to blockage [10], this patient maybe having breathing difficulties that led to oxygen demand as well as glucose demand to carry out a proper respiration process [11]. The average blood glucose of patient 5113 is 4.4 U/hour from the demographic.

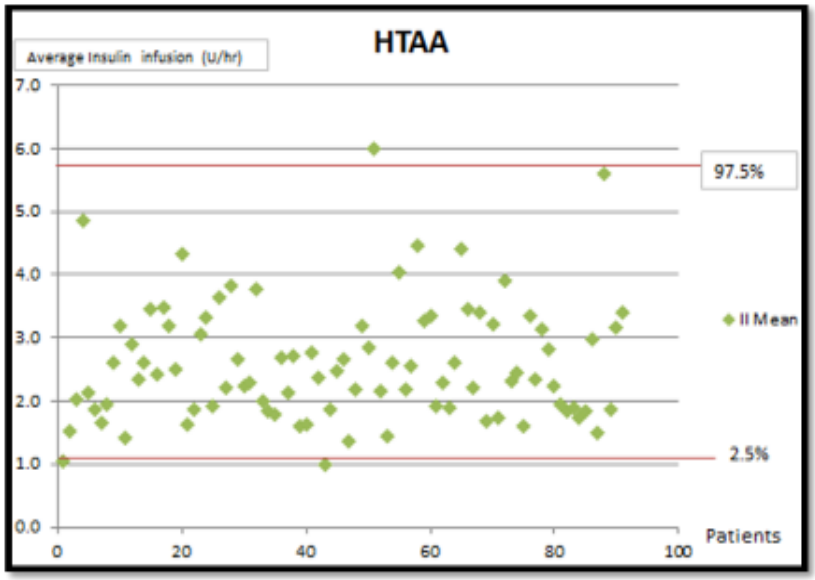

Figure 3**:** Average Insulin Infusion for HTAA

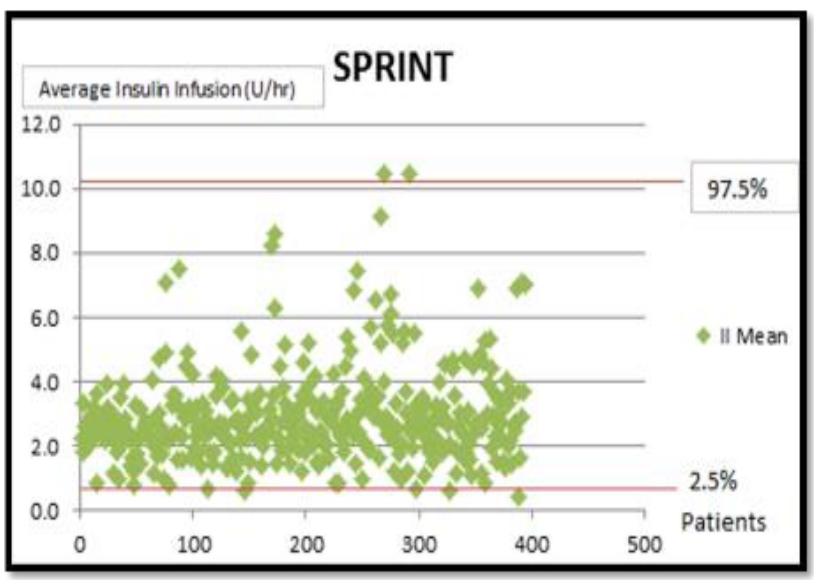

Figure 4**:** Average Insulin Infusion for SPRINT

Based on Figure 3, for HTAA protocol, most of the average insulin infusion data are within the interval of 97.5% (Q_3) and 2.5% (Q_1) for 95% confidence interval. Out of 91 patients, it is found that 87 patient's average insulin infusion data are within the line intervals. There are 3 patients data are out of range where 1 is beyond 97.5 % line while the rest are below 2.5% line. There might be a chance that the average insulin infusion amount suits based on the average blood glucose of patients. On SPRINT protocol referring Figure 4, most of the average insulin infusion data are within the interval of 97.5% (Q_3) and 2.5% (Q_1) for 95% confidence interval. Out of 394 patients, it is found that 391 patient's average insulin infusion data are within the line intervals. There are 3 patients data are out of range where 2 are beyond 97.5 % line while 1 is below 2.5% line. Equal number of outliers been found in both plots. But, the data's significant level is still undefined, with only scatter plot doesn't shown any strong evidence of how significant it is.

Table 5**:** Insulin Infusion Analysis (HTAA)

HTAA Protocol Insulin Infusion Statistical Analysis	
Mean	2.59
Standard Error	0.10
Median	2.36
Mode	2.26
Standard Deviation	0.94
Sample Variance	0.89
Kurtosis	1.73
Skewness	1.13
Range	5.01
Minimum	0.99
Maximum	6.00
Sum	235.93
Count	91.00
Third Quartile,Q3 (97.5%)	5.80
First Quartile,Q1(2.5%)	1.19

Table 6**:** Insulin Infusion Analysis (SPRINT)

SPRINT Protocol Insulin Infusion Analysis	
Mean	2.90
Standard Error	0.07
Median	2.65
Mode	2.00
Standard Deviation	1.44
Sample Variance	2.07
Kurtosis	5.65
Skewness	1.89
Range	10.06
Minimum	0.41
Maximum	10.47
Sum	1141.83
Count	394
Third Quartile,Q3(97.5%)	10.33
First Quartile,Q1(2.5%)	0.55

Based on table 5, for HTAA protocol, the grand mean, $\bar{X}$ for the insulin infusion is 2.59 U/hour while Q_2 and Mo are 2.36 U/hour and 2.26 U/hour respectively. Q_1 and Q_3 for 95 % confidence interval are 1.19 U/hour and 5.80 U/hour. In terms of measuring the central tendency, this data is in such way mode < median < mean. Hence, the values for 95 % confidence interval are 2.26 U/hour [1.19 U/hour, 5.8 U/hour]. The patient's data which are consider as outlier are extracted from the patients demographic and tabulated for average insulin infusion of HTAA protocol as shown below.

Table 7: Outlier Data

Patient Code	Age	Gender	Ethnicity	BMI	Diagnosis	Death
G001	77	Male	Malay	24.2	Pneumonia	Yes
G043	62	Male	Malay	22.2	Leptospirosis	No
G051	18	Female	Malay	30.5	Allergy	No

Based on table 7, patient G001 suffers from pneumonia, which is an inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli [13]. Probably of breathing difficulties and considering twilight age, there could be possibilities of organ malfunction may lead to high insulin demand instead of 1 U/hour. However, the patient's BMI considered as normal but already faced mortality. Patient G043 suffers from Leptospirosis same as patient G065, as it is a blood related disease [9]. However this patient's BMI consider as healthy, since this patient undergoes dialysis, there is a probability of high insulin demand considering the twilight age and kidney malfunctions issue [14]. Patient G051 at the age of 18 suffers from allergic but now mention specifically in patients demographic, but her BMI is 30.5 indicates that she is obese. According to table 6, the grand mean, $\bar{X}$ for the insulin infusion is 2.9 U/hour while Q_2 and Mo are 2.65 U/hour and 2.00 U/hour respectively. Q_1 and Q_3 for 95 % confidence interval are 0.55 U/hour and 10.33 U/hour. In terms of measuring the central tendency, this data is in such way mode < median < mean. Hence, the values for 95 % confidence interval are 2.65 U/hour [0.55 U/hour, 10.33 U/hour]. The patient's data which are consider as outlier are extracted from the patients demographic and tabulated for average insulin infusion of SPRINT protocol as shown below.

Table 8: Outlier Data

Patient Code	Age	Gender	Diagnosis Code
5270	48	Female	RPR
5291	59	Male	TBF,TA
5388	75	Male	GCC

Based on table 8, patient 5270 is a female with an age of 48 suffers from restrictive lung disease, disorder of lungs parenchyma where the normal lungs tissue become scar [15]. This could be due to breathing difficulties or less glucose level in the body caused to have an excessive insulin infusion. Patient 5291 is a male with an age of 59, suffers from abdomen problem

together with trauma related to femur (bone/skeleton). Patient 5388 is a male with the age of 75 suffers from gastrointestinal colon. This patient suffers from food digestion problems [16] which cause high insulin demand.

Linear Regression and Mann-Whitney Analysis

Linear regression analysis is used to compare between two variables 'X' and 'Y'. In order to find out how close the data is fitted to the regression, finding R squared value also knows as coefficient of determination is necessary. Generally, R-squared value indicates the proportion of the variance in the dependent variable, Y that is predictable from the independent variable, X [17]. The variables been compared in such way between the average blood glucose of patients for both hospitals and insulin infusion of patients as well for both hospitals, since the number of samples for variable X and Y must be equal [17], the number of patients from Christchurch involve in this analysis are only 91 out of 394 making equal to the number of patients in HTAA. Theoretical study shows that R-squared value greater than 0.5 or 50% brings the meaning of variables X and Y have a greater correlation and dependent each other [18]. In the end of the subtopic, the R-squared value is required to solidify the statement assumed for the goal of both protocols. The assumption has been made in such way:

$$R^2 > 0.5, \quad Both\ HTAA\ and\ SPRINT\ protocols\ might\ be\ similiar\ in\ their\ goal$$

$$R^2 < 0.5, \quad Both\ HTAA\ and\ SPRINT\ protocols\ might\ not\ be\ similiar\ in\ their\ goal$$

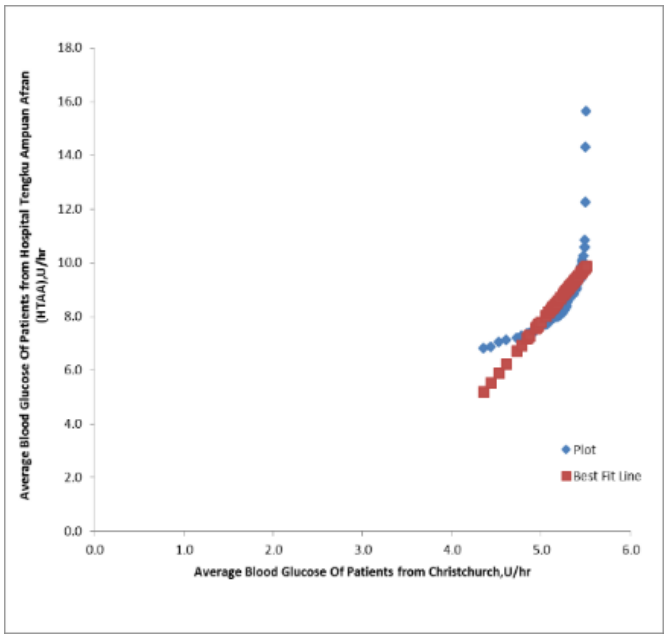

Figure 5**:** Regression Graph of Average Blood Glucose

On Figure 5, the blue line represents the plot for average blood glucose of patients upon axis X: Christchurch and Y: HTAA. The red line is the best fit linear line for the plotted data. It has been found that the red line passes most of the plotted data showing that gradient of the linear line very significant together with the data.

Table 9**:** Summary Output of Average Blood Glucose for HTAA and SPRINT

Regression Statistics	
Multiple R	0.71529
R-Squared	0.51164
Adjusted R-Squared	0.50615
Standard Error	0.98966
Observations	91

Based on Table 9, for 91 (observations) patients from both HTAA and Christchurch hospitals throughout the regression analysis done by using

Microsoft Excel, the R-squared value obtained is 0.51164 or 51.16% while the standard error is 0.98966. The R-squared value obtained is greater than the assumed value which is 0.5. Therefore, there is a probability that both protocols might be same in their goal, since there is a strong correlation between those two variables (X: SPRINT, Y: HTAA) protocols about 51.16% showing that the regression line fit the data. However, to valid the statement, another regression analysis has been done for average insulin infusion of patients.

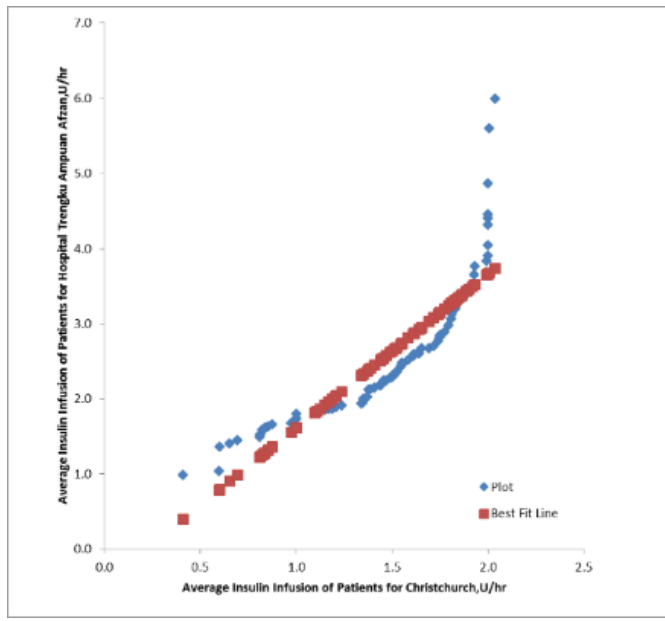

Figure 6**:** Regression Graph of Average Insulin Infusion

On Figure 6, the blue line represents the plot for average insulin infusion of patients upon axis X: Christchurch and Y: HTAA. The red line is the best fit linear line for the plotted data. It has been found that the red line passes least of the plotted data showing that gradient of the linear line less significant together with the data.

Table 10**:** Summary Output of Average Insulin Infusion for HTAA and SPRINT

Regression Statistics	
Multiple R	0.88041
R-Squared	0.77512
Adjusted R-Squared	0.77260
Standard Error	0.45044
Observations	91

Based on Table 10, for 91 (observations) patients from both HTAA and Christchurch hospitals throughout the regression analysis done by using Microsoft Excel, the R-squared value obtained is 0.77512 while the standard error is 0.45044. The R-squared value obtained is greater the assumed value which is 0.5. A strong correlation of 77.51 % between the two variables (X: SPRINT, Y: HTAA) protocols can be defined both of them are depend each other in addition of line fitting the data.

Therefore, $R^2 > 0.5$ both HTAA and SPRINT protocols might be same in their goal is a valid and acceptable statement.

One Way Analysis of Variance (ANOVA) Table and Mann-Whitney

ANOVA table has been applied in this project assuming the mode ≈median≈mean [19] since there is no huge difference in these values because been locate in the modal class, hence all the histogram shapes assume to be normally distributed. This table been used to find the p-values in order to determine whether the data is significant or not, but generally p-value is used to observe result to a relative statistical model on how extreme the observation is. In addition, p-value is defined as the probability of obtaining a result equal to or "more extreme" than what was actually observed, assuming that the model is true [20]. In this study, the ANOVA table been generated under 95% confidence interval in Microsoft Excel, hypothesis statement has been made in such way:

$$p > 0.05, \quad The\ data\ is\ not\ significant$$
$$p < 0.05, \quad The\ data\ is\ significant$$

Table 11**:** ANOVA for Average Blood Glucose

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F critical*
Between Groups	413.4228	1	413.4228	201.3941	1.8622E-38	3.8608
Within Groups	991.5050	483	2.0528			
Total	1404.9278	484				

Based on Table 11, the p-value for the average blood glucose obtained is 1.8622E-38 which is less than 0.05. Hence, $p > 0.05$ the average blood glucose data is significant considered valid and acceptable. The average blood glucose of patients are adapted to respective implemented protocols.

Table 12**:** ANOVA Analysis for Average Insulin Infusion

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F critical*
Between Groups	6.8947	1	6.8947	3.7261	0.05415	3.8608
Within Groups	893.7303	483	1.8504			
Total	900.6250	484				

Based on Table 12, the p-value for the average insulin infusion obtained is 0.05415 which is greater than 0.05. Hence, $p > 0.05$ the average insulin infusion data is not significant, this statement is valid and acceptable. Might be the insulin infusion is imbalance due to patient's health condition or illness related to blood.

Conclusion

Based on the result obtained in terms the scatter plot, all 4 data looks significant and most of the plots are within 95% confidence interval line of Q_1 and Q_3 quartile, only few outliers can be found in each data. The outlier patient's data have been extracted and analyzed according to Body Mass Index (BMI), age, gender, and diagnosis for behaving in such way. When it comes to the central tendency measurement, all data are in such way $Mo < Q_2 < \bar{X}$ and the positively skewed shape has been proven by the descriptive statistic. It has been found the mode, mean, and median are lies within the modal class. In order to carry out ANOVA table, an assumption has been

made in a way $Mo \approx Q_2 \approx \bar{X}$ since all the value approaches the modal class, hence later all the histograms shape is assumed to be normally distributed. Regression analysis has been done on average blood glucose and average insulin infusion in order obtained the R-squared value, it has been found that both R-squared values obtained are greater than 0.5 proving the statement of HTAA and SPRINT protocols are same in their goal and function. In ANOVA table, the p-value obtained from average blood glucose is less than 0.05 showing the data is significant, on the other hand for average insulin infusion is greater than 0.05 means the data is not significant. By comparing the patients from Christchurch Hospital, New Zealand and Tengku Ampuan Afzan, Malaysia (HTAA), it is very obvious the insulin infusion data could be less significant due to environmental factor, ethnicity, height, weight, and lifestyle.

Recommendation

Since both protocols are same in their goal, it is possible for these hospitals to exchange their protocols by term of collaboration as there is an evidence of both protocols are same in achieving the goal . It has been found both HTAA and Christchurch hospital achieve the target in respective way. However, both protocols are not capable to prevent the mortality rate but can reduce it as proven in previous case study. Therefore, by taking in account the environmental factor, ethnicity, height, weight, and lifestyle, both SPRINT and HTAA protocols are suitable for Malaysian critically ill patients and can be widely implement in all hospitals.

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