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Association between Diabetes Mellitus and Sepsis for the Glycemic Control Outcome of Two Intensive Care Units in Malaysia

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Abstract: Close monitoring and tight glycemic control are required among critically ill patients as they have dynamic metabolism which may precipitate stress-induced hyperglycemia. Clinically, diabetes mellitus (DM) patient with sepsis indicated a high mortality rate. This study investigates the association between DM and non-DM related to sepsis and non-sepsis patients from different insulin infusion therapy management. This study used 128 retrospective data from Hospital A, and 37 retrospective data from Hospital B. ICU patients who received insulin infusion therapy during their stay in the ICU were selected. Both centres implement the sliding scale-based insulin infusion therapy with the target range for blood glucose (BG) level within 6.0 - 10.0 mmol/L. The retrospective clinical data were compared among cohorts for DM and non-DM associated with sepsis and non-sepsis conditions. Findings showed that the DM group had higher insulin sensitivity than non-DM for both cohorts. Meanwhile, cohort B had higher insulin sensitivity than cohort A for all classes. Cohort A (DM+Sepsis) had low insulin sensitivity (66.7 L/(mU.min) and worst condition with sepsis which resulted from the lowest percentage (30.81%) of BG measurement within the target range. The (nonDM+nonSepsis) class had the tightest glycemic control for cohort A (3.4 mmol/L) and cohort B (2.2 mmol/L), as observed by the BG interquartile range. Furthermore, cohort A (nonDM+nonSepsis) had a 41.55% of severe hyperglycemia and 0.12% for severe hypoglycemia. Contrary, cohort B (nonDM+nonSepsis) had the highest percentage within the target range (74.31%) and the lowest percentage of hyperglycemia (18.78%). There was significantly different (p-values <0.05) between cohort A and cohort B in BG level and glucose intake, likewise between sepsis and non-sepsis of non-DM for both cohorts. The findings indicate that a successful glycemic control protocol is much influenced by insulin sensitivity, patient variability, diabetes condition, and patient sepsis status.

Keywords: Glycemic control, critically ill patient, diabetes mellitus, sepsis

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1. Introduction

Controlling blood glucose (BG) level among intensive care patient is very challenging. Critically ill patient with or without diabetic background may experience stress-induced hyperglycemia during their stay in the intensive care unit (ICU). Hyperglycemia may exacerbate the outcomes like severe infection and sepsis. Moreover, hyperglycemia also increases the risk of mortality and morbidity among critically ill patients [1]. In addition, diabetes mellitus (DM) patient with sepsis indicated higher mortality than non-diabetic groups. They are also prone to insulin resistance due to increased counter-regulatory hormones concentrations [1-4]. The ICU patients without DM history who experienced hyperglycemia in the ICU are a significant independent risk factor contributing to hospital mortality [5]. Therefore, critically ill patients require high monitoring and tight glycemic control during their stay in the ICU.

Insulin therapy able to control stress-induced hyperglycemia among critically ill patient. There are many protocols exist in managing the glycemic level for critically ill patients, including sliding scale-based and model-based control [6-9]. In Malaysia, most ICU implements the insulin infusion protocol by applying a sliding scale-based to control the glycemic level. When using the sliding scale, the therapy management and change of scale are not the same among centres. Thus, the patient outcome may vary due to the variation in scale selections. The BG level needs to be controlled within 6.0-10.0 mmol/L based on the Malaysian Ministry of Health (MOH) guideline [10]. This BG target is similar to the American Diabetes Association (ADA) target [11].

Furthermore, each patient has different dynamic metabolism and insulin sensitivity level, which may respond differently to the treatment given to them. Sepsis patients typically have lower insulin sensitivity compared to non-sepsis patients [12, 13]. The response towards insulin administration can be determined by investigating the insulin sensitivity of the ICU patient. This study used the glucose-insulin model to generate the insulin sensitivity profiles of the patient. This model has been validated and has been used in several studies [12, 14-17]. The insulin sensitivity profiles obtained can be used to analyse the characters and predict the patient's response toward insulin therapy. BG measurement, insulin administration, and glucose intake of the patients from retrospective clinical data were fitted in the model.

This work investigates the outcome of two insulin infusion therapy in two ICUs in Malaysia, Hospital Universiti Sains Malaysia (HUSM) and University Malaya Medical Centre (UMMC). Patient demographic and insulin sensitivity were compared among the two cohorts to analyse the patient variability aspects. A comparison was also made between DM and non-DM associated with sepsis and non-sepsis condition among the patients.

2. Methodology

2.1 Retrospective Data

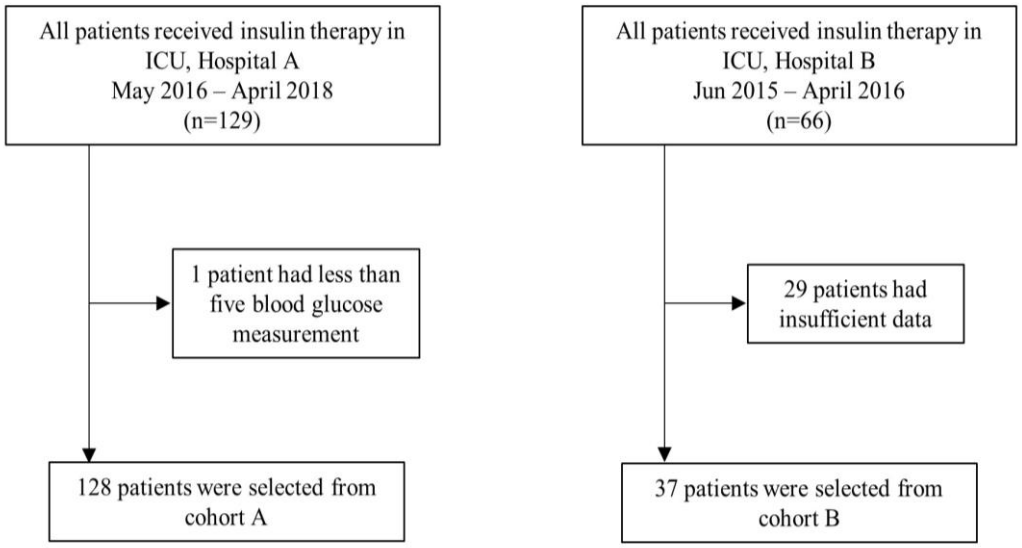

Fig. 1 - Retrospective data selection of ICU patients in cohort A and cohort B

The retrospective clinical data were obtained from the Intensive Care Unit, Hospital Universiti Sains Malaysia (HUSM), between May 2016 and April 2018, and Intensive Care Unit, University Malaya Medical Centre (UMMC), between Jun 2015 and April 2016. The ethical approval was obtained from the Universiti Sains Malaysia Human Research Ethics Committee. The patient who received the insulin infusion therapy during their stay in the ICU, with and without diabetic background and had at least five BG measurement been selected. In this study, the patient from

HUSM was represented as cohort A while the patient from UMMC as cohort B. The data selection for this study is depicted in Fig. 1.

Originally, the total number of patients collected from cohort A were 129 patients, while cohort B were 66 patients. However, one patient from cohort A had less than five BG measurements, and 29 patients from cohort B who had insufficient data for analysis were eliminated. Thus, cohort A consists of 128 patients, and cohort B consists of 37 patients. The clinical data were compared between cohort A and cohort B with DM and non-DM associated with sepsis and non-sepsis patients.

Demographic data for cohort A and cohort B can be seen in Table 1. Cohort B had older patients with age median of 65 years old compared to cohort A, 60 years old. The percentage of male patients and DM patients for cohort A were 58% and 22%, respectively. Cohort B had 70% male patients and 65% DM patients.

Table 1 - Demographic data of ICU patients in cohort A and cohort B

	Cohort A	**Cohort B**
Number of patients	128	37
Percentage of males (%)	58	70
Percentage of DM patients (%)	22	65
Age median [IQR] (years)	60 [52 - 67]	65 [56 - 73]

2.2 Insulin Infusion Therapy

Both centres implemented insulin infusion protocol based on the sliding scale-based method, as shown in Fig. 2. Furthermore, both centres targeted the BG to be controlled within 6.0 - 10.0 mmol/L. However, the therapy management was different between the centres. Protocol A and Protocol B started the insulin infusion therapy with Scale 2 when the BG level is more than 10 mmol/L. The difference between Protocol A and Protocol B is the scale changes when the BG level is maintained or higher than the previous level. Protocol A increased the scale by two columns to the right, while Protocol B increased the scale by one column to the right. Both protocols monitored the BG measurement hourly until it reached the target. On the other hand, the scale is maintained for both protocols when the BG within the target range and the BG level will be monitored every 4 hours for Protocol A and every 2-4 hours for Protocol B. If the BG value is below the target, less than 5 mmol/L for Protocol A and less than 4 mmol/L for Protocol B, intravenous insulin infusion is ceased, and the nurse has to inform the doctor immediately.

Blood glucose (mmol/L)		**Scale 1 (U/h)**	**Scale 2**	**Scale 3**	**Scale 4**	**Scale 5**	**Scale 6**	**Scale 7**	**Scale 8**
Protocol A	**Protocol B**								
≥ 22.1	**≥ 22.1**	3.0	4.0	5.0	6.0	7.0	8.0	10.0	11.0
18.1-22	**18.1-22**	2.5	3.5	4.0	5.0	6.0	6.0	8.0	9.0
14.1-18	**14.1-18**	2.0	3.0	3.0	4.0	5.0	5.0	6.0	7.0
12.1-14	**12.1-14**	1.5	2.5	2.5	3.0	4.0	4.0	4.0	5.0
10.1-12	**10.1-12**	1.0	2.0	2.0	2.0	3.0	3.0	3.0	4.0
8.1-10	**8.1-10**	1.0	1.0	1.0	1.5	2.0	2.0	2.5	3.0
6.1-8	**6.1-8**	0.5	1.0	1.0	1.0	1.5	1.5	2.0	2.0
5.1-6	**5.1-6**	0.5	0.5	0.5	0.5	1.0	1.0	1.5	1.5
< 5	**< 4**	Cease IV insulin infusion and inform doctor							

Fig. 2 - Sliding scale-based of insulin infusion therapy for Protocol A and Protocol B

2.3 Glucose-Insulin Model

A validated glucose-insulin model established from another study has been used to identify the insulin sensitivity profiles of the patient [12, 14-19]. Among the input parameters are BG concentration, insulin infusion administration, and glucose intake rate of the patients. Details of the equations of the glucose-insulin model and the nomenclature can be referred in this article [20, 21]. The insulin sensitivity represents the patient-specific sensitivity or parameter that correspond to the insulin therapy received. It indicates the body cells sensitivity in response to insulin [22].

3. Results and Discussion

The cumulative distribution function (CDF) of insulin sensitivity for cohort A and cohort B with a group of DM and non-DM are shown in Fig. 3. Cohort A had more variation of patient's metabolism compared to cohort B for both DM and non-DM groups, which can be seen from a more extensive range between the lower and upper bound of the CDF. However, cohort B had higher insulin sensitivity compared to cohort A though it had a steeper slope CDF of insulin sensitivity for DM and non-DM groups. The findings were in line with previous study [21]. At 50% CDF, the median insulin sensitivity for cohort A with DM is 6.49 L/(mU.min), whereas non-DM is muchly lower and starting to increase at 60% CDF with 1.14 L/(mU.min). The median insulin sensitivity for cohort B with DM is 23.30 L/(mU.min), whereas non-DM is 12.31 L/(mU.min). DM patients had higher insulin sensitivity than non-DM, as seen from this figure. This potentially due to the non-DM cohort that suffers other medical conditions such as severe sepsis or septic shock.

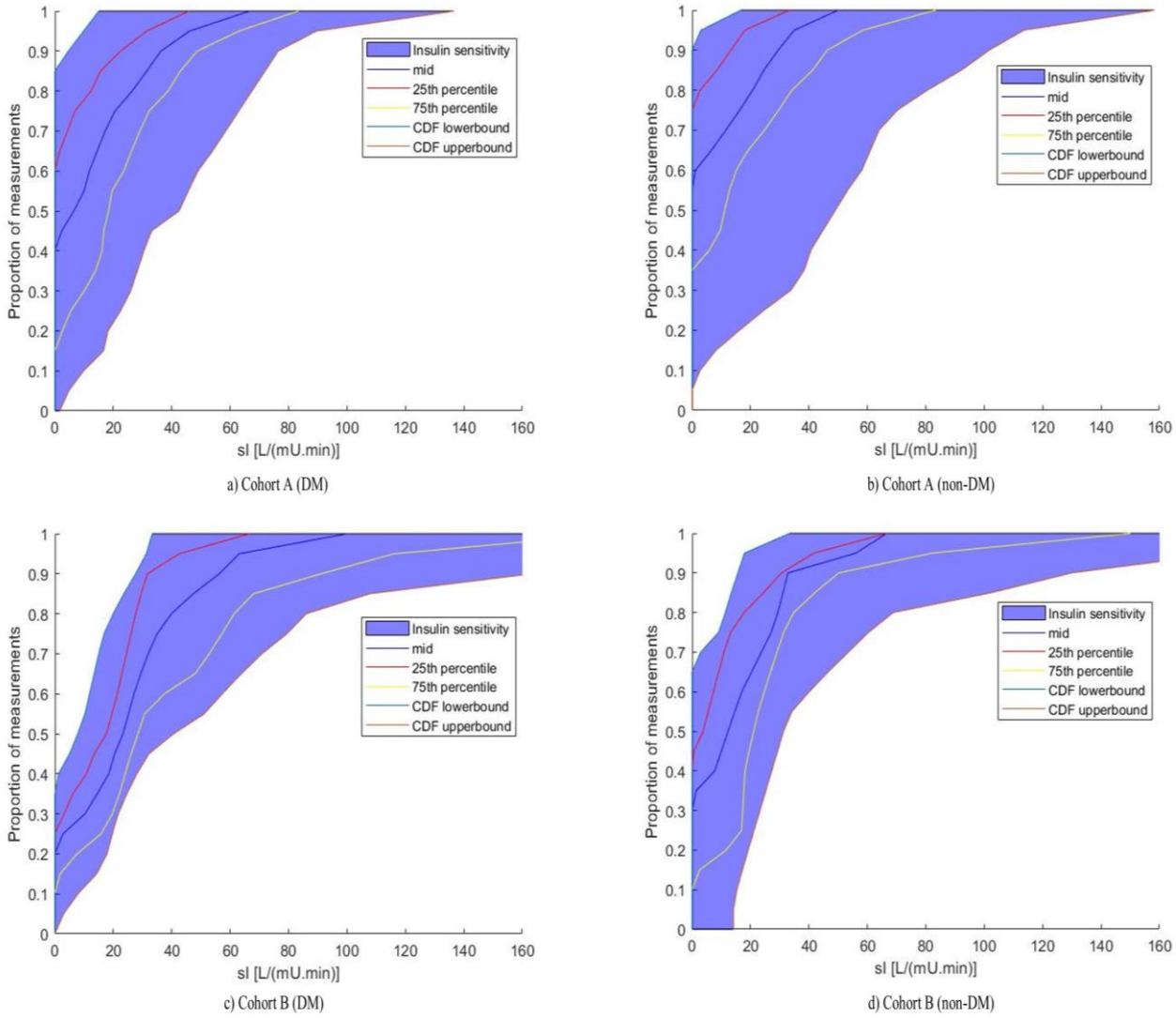

Fig. 3 - Insulin sensitivity CDF of cohort A and cohort B for different groups: a) cohort A (DM), b) cohort A (non-DM), c) cohort B (DM), and d) cohort B (non-DM)

Table 2 shows the comparison between the outcome of insulin infusion therapy for cohort A and cohort B according to several patient classifications. Patients were classified based on diabetic status (DM and non-DM) and sepsis condition (sepsis and non-sepsis). All groups from both cohorts have a one-hour interval of BG measurement. Cohort A (DM+Sepsis) achieved median BG of 11.2 mmol/L, which is the highest among the other groups, eventhough they received quite a high dose of insulin with a median of 1.8 U/hr. Moreover, the percentage of measurement within the target range was the least, which is 30.81% and the highest percentage of BG measurement greater than 10 mmol/L, with 66.9%. Similarly, (DM+Sepsis) had the most elevated median BG of 9.3 mmol/L among cohort B classes. It also achieves the lowest percentage of measurement within target for cohort B classes, with 52.22% and the highest percentage of BG measurement greater than 10 mmol/L, with 35.94%. Furthermore, the findings from this study showed the median BG for (DM+Sepsis) class, 11.2 mmol/L (cohort A) and 9.3 mmol/L (cohort B), are higher than (nonDM+Sepsis) class, 9.1 mmol/L (cohort A) and 8.2 mmol/L (cohort B). This results in line with the study done by S. Lin *et al.* [4].

Comparing the same class of (DM+sepsis) for cohort A and B, cohort B had better control because median BG is within the target range and less percentage of measurement over the target compared to cohort A. However, it can be seen that cohort B received a higher rate of insulin which is 2.2 U/hr, compared to cohort A with 1.8 U/hr. (DM+Sepsis) patients in both cohorts were incapable of controlling the BG level within the target range of 6.0 - 10.0 mmol/L eventhough they received a higher dose of insulin. This indicates that the patients with DM and sepsis were not responding well to the insulin treatment given to them. Other study also reported that DM with sepsis patient had a high mortality rate [2].

Table 2 - Comparison between cohort A and cohort B with classes of DM+Sepsis, DM+nonSepsis, nonDM+Sepsis, and nonDM+nonSepsis

	Cohort A				**Cohort B**			
	DM + Sepsis	**DM + nonSepsis**	**nonDM + Sepsis**	**nonDM + nonSepsis**	**DM + Sepsis**	**DM + nonSepsis**	**nonDM + Sepsis**	**nonDM + nonSepsis**
Number of patients:	6	22	42	58	15	9	4	9
Total hours:	867 hours	2863 hours	6310 hours	7330 hours	1852 hours	1164 hours	506 hours	1221 hours
Total number of BG measurement:	873	2885	6352	7388	1867	1173	510	1230
Median BG (cohort) [IQR] (mmol/L):	11.2 [9.5 - 13.4]	9.8 [8.0 - 11.9]	9.1 [7.5 - 10.9]	9.5 [7.9 - 11.3]	9.3 [7.6 - 11.1]	8.9 [7.5 - 10.8]	8.2 [7.1 - 10.2]	8.4 [7.3 - 9.5]
Median insulin rate per-patient (U/hr):	1.8 [0.8 - 2.6]	1.0 [0.5 - 1.4]	0.6 [0.2 - 1.1]	0.8 [0.5 - 1.8]	2.2 [1.6 - 2.9]	1.9 [1.1 - 2.6]	1.3 [0.9 - 2.5]	1.5 [1.0 - 1.8]
Median glucose rate per-patient (g/hr):	0.6 [0.0-1.5]	2.0 [0.7 - 3.4]	1.2 [0.2 - 2.4]	2.2 [0.6 - 3.2]	1.7 [0.7 - 3.6]	1.1 [0.5 - 3.3]	0.3 [0.0 - 0.9]	6.2 [3.5 - 10.1]
Median insulin sensitivity [IQR] (L/(mU/min)):	66.7 [66.7-100.0]	58.3 [33.3-83.3]	50.0 [33.3-66.7]	66.7 [33.3-100.0]	100.0 [66.7-195.8]	100.0 [58.3-150.0]	150.0 [66.7-216.7]	66.7 [66.7-108.3]
% measurement BG < 2.2	0.00	0.00	0.06	0.12	0.11	0.00	0.00	0.00
% measurement BG < 6.0	2.29	6.72	10.58	5.55	7.55	6.65	6.27	6.50
% measurement 6.0 ≤ BG ≤ 10.0	30.81	46.03	52.74	52.64	52.22	60.27	66.86	74.31
% measurement BG > 10.0	66.90	47.14	36.67	41.55	35.94	32.91	26.47	18.78

Meanwhile, other classes able to control the BG level within the target range. Comparing the classes of (DM+nonSepsis) and (nonDM+Sepsis) for both cohorts, it can be seen that (nonDM+Sepsis) achieved tighter control with median BG lower than (DM+nonSepsis) class, as expected. Besides, the percentage of measurement within the target range is 52.74% (nonDM+Sepsis) compared to 46.03% (DM+nonSepsis) for cohort A, and 66.86% (nonDM+Sepsis) compared to 60.27% (DM+nonSepsis) for cohort B. (DM+nonSepsis) class for both cohorts received a higher dose of insulin, which are 1.0 U/hr and 1.9 U/hr, for cohort A and B, respectively, compared to 0.6 U/hr and 1.3 U/hr for (nonDM+Sepsis) class.

From Table 2, (nonDM+nonSepsis) of cohort B had the tightest glycemic control with the BG interquartile range of 2.2 mmol/L and median BG of 8.4 mmol/L, followed by (nonDM+Sepsis) class with BG interquartile range of 3.1 mmol/L, (DM+nonSepsis) with 3.3. mmol/L, and (DM+Sepsis) with 3.5 mmol/L for cohort B. Similarly, for cohort A, the tightest BG interquartile range is (nonDM+nonSepsis) with 3.4 mmol/L, followed by (nonDM+Sepsis) with 3.4 mmol/L, (DM+nonSepsis) with 3.9 mmol/L, and (DM+Sepsis) with 3.9 mmol/L. The similar trend of interquartile range among the classes means that tighter control is more achievable for (nonDM+nonSepsis) class compared to other classes. However, it is easier to control sepsis patients compared to DM patients.

DM patients received higher insulin rate than non-DM patients for both cohorts. Cohort A (DM+Sepsis) received 3x insulin of cohort A (nonDM+Sepsis), while cohort B (DM+Sepsis) received almost 1.7x insulin of cohort B (nonDM+Sepsis). For (nonDM+nonSepsis) class, they achieved higher BG level than (nonDM+Sepsis) class among their cohorts though they received an average value of insulin rate. This is mainly due to (nonDM+nonSepsis) classes had higher glucose intake compared to (nonDM+Sepsis) classes, indicating a trade-off between insulin and glucose intake for controlling the glycemic level of the patients.

Additionally, although cohort A (nonDM+nonSepsis) able to control the BG within the target range but it had the highest severe hypoglycemia event among the cohorts with the percentage of BG less than 2.2 mmol/L was 0.12%. In contrast, cohort B (nonDM+nonSepsis) had no BG measurement less than 2.2 mmol/L. Moreover, this class also had the highest percentage (74.31%) of BG measurement within the target range of 6.0 - 10.0 mmol/L, and had the lowest percentage (18.78%) of BG measurement more than 10.0 mmol/L. Meanwhile, cohort A (DM+Sepsis) had the lowest percentage (30.81%) among the cohorts for BG measurement within the target range. In addition, cohort A (DM+Sepsis) had more hyperglycemia event during their stay in the ICU with the highest percentage (66.90%) of BG level greater than 10.0 mmol/L. These results showed that cohort A (DM+Sepsis) had low insulin sensitivity exacerbated with sepsis conditions, consequently not responding well to the treatment. Comparing the same class between two cohorts, cohort B has better outcome in terms of the median and interquartile BG. Besides the percentage of BG measurement within the target range indicates that the protocol adapted on cohort B able to achieve better outcome than cohort A.

Fig. 4 shows the graphs of BG, insulin, and feed CDF for cohort A and cohort B. Additionally, Table 3 shows the statistical analysis of BG, insulin, and feed for this study's classes and cohorts. From Fig. 4(a), the BG level of cohort A was more varied than cohort B as patients in cohort A had a lower insulin sensitivity. Cohort A (DM+Sepsis) had the highest BG measurement at 50% of BG CDF compared to other groups, followed by cohort A (DM+nonSepsis), cohort B (DM+Sepsis), and cohort B (DM+nonSepsis). There is a significant difference between BG of cohort A and cohort B for both non-sepsis and sepsis of non-DM patients ($p=0.00$ and $p=0.04$). Nevertheless, BG of cohort A and B were not significantly different with p-values >0.05 for DM class, as depicted in Table 3.

The insulin CDF from Fig. 4(a) showed that cohort A (DM+Sepsis) and cohort B (DM+nonSepsis) intersected at 50% insulin CDF with 1.67 U/hr. Even though cohort A (DM+Sepsis) received higher insulin than cohort A (DM+nonSepsis), they could not control the BG within the target range due to relatively low insulin sensitivity and not responding well toward the treatment given to them. Furthermore, cohort B (DM+Sepsis) had the highest insulin rate of 2.21 U/hr at 50% CDF. Even though this cohort received high insulin, they did not result in the lowest BG measurement at 50% BG CDF because they had high glucose intake, which counteracted the BG level to be the lowest among cohorts. There is a significant mean difference between cohort A (DM+nonSepsis) and cohort B (DM+nonSepsis) for insulin rate with p-value <0.05 ($p=0.03$). Additionally, there is a significant difference ($p=0.04$) between non-sepsis and sepsis of non-DM class for cohort A insulin rate.

Fig. 4 also shows the graph of feed CDF, which represents the glucose intake in the cohorts. At 50% feed CDF, the non-sepsis class had higher glucose intake compared to the sepsis class for both cohort A and cohort B. There was no significant mean difference in glucose intake for both cohorts in the DM class, as shown in Table 3. However, there is a significant difference between cohort A and B for non-sepsis ($p=0.04$) and sepsis ($p=0.01$) classes of non-DM.

For the non-DM class on the right panel of Fig 4(b), the BG measurement for all cohorts was within the target range at 50% CDF. Besides, cohort A received a lower insulin rate than cohort B for sepsis and non-sepsis classes, as can be seen from Fig. 4(b)(2). Cohort B (nonDM+nonSepsis) was well responded towards the insulin treatment though they had the highest glucose intake, they manage to control the BG level (8.4 mmol/L) within the target range with high insulin treatment given to them.

Overall, there was a significant mean difference (p-values <0.05) for BG level and glucose intake (feed) between cohort A and cohort B, as well as between sepsis and non-sepsis of non-DM for both cohorts. For insulin rate, there was a significant difference between non-sepsis and sepsis for cohort A (non-DM) with p=0.04, while other classes were not significantly different.

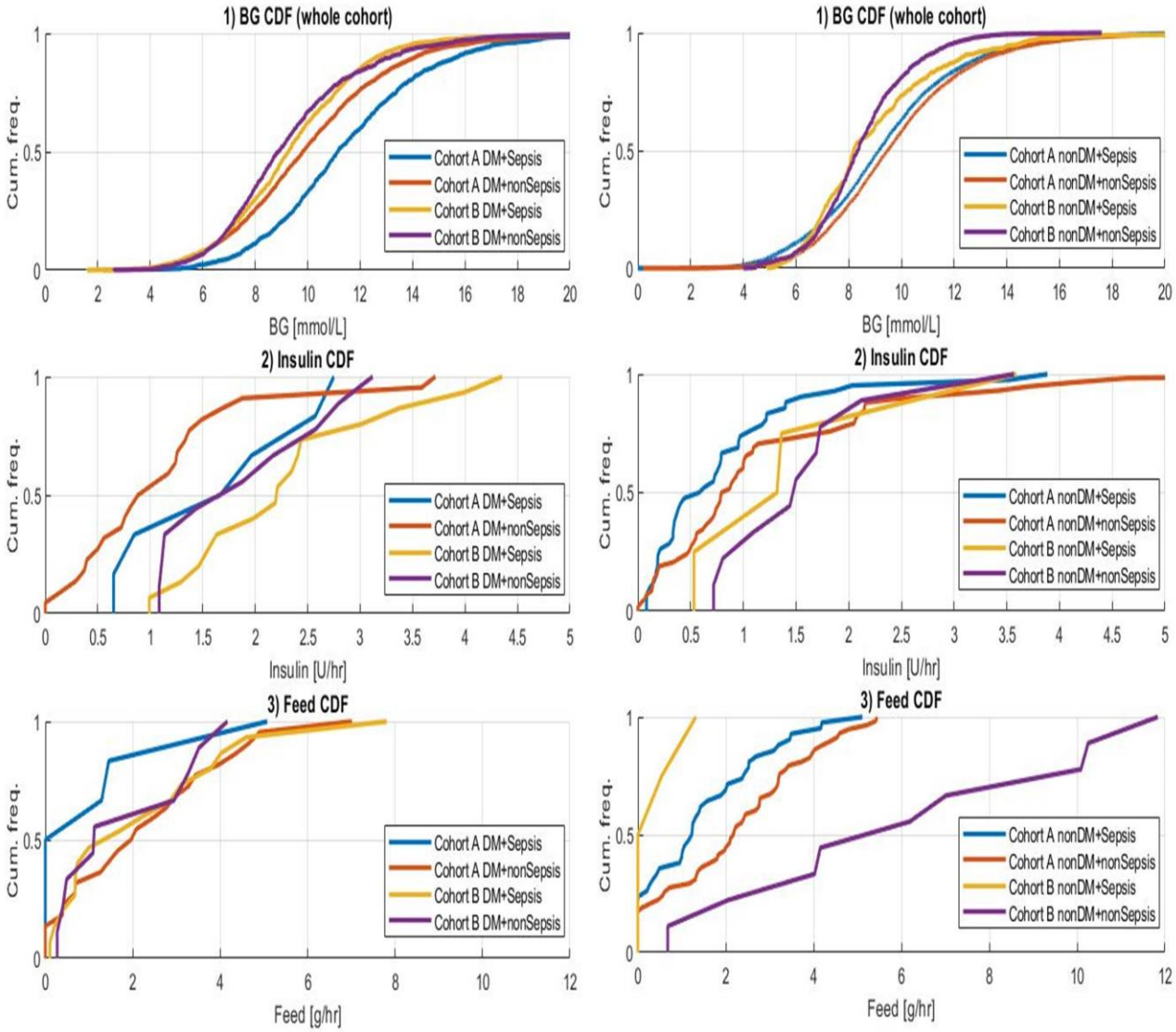

Fig. 4 - CDF of blood glucose, insulin, and feed of cohort A and cohort B for a) DM and b) non-DM groups

Table 3 - p-values of blood glucose, insulin, glucose intake for both cohorts

	BG			Insulin			Feed		
	Cohort A Vs Cohort B	Cohort A	Cohort B	Cohort A vs Cohort B	Cohort A	Cohort B	Cohort A vs Cohort B	Cohort A	Cohort B
DM+nonSepsis	0.79	0.87	0.52	0.03	0.24	0.24	0.32	0.44	0.61
DM+Sepsis	0.79			0.13			0.62		
nonDM+nonSepsis	0.00	0.00	0.01	0.34	0.04	0.91	0.04	0.01	0.00
nonDM+Sepsis	0.04			0.30			0.01		

4. Conclusion

Controlling the glycemic level among ICU patients in clinical settings is very challenging due to the patient's dynamic metabolism. Insulin sensitivity of the patient able to indicate the patient's variation in the cohort. This study showed that cohort A had lower insulin sensitivity than cohort B and DM class had higher insulin sensitivity than the non-DM class for both cohorts. Cohort A (DM+Sepsis) had the lowest BG percentage within the target (30.81%), indicating the BG level not being adequately controlled within the target range of 6.0-10.0 mmol/L. Despite low insulin sensitivity value, this class of patients also developed sepsis, which worsens the condition. Furthermore, non-DM cohorts could control the BG level within the target though they received a lower insulin rate and had higher glucose intake compared to the DM cohorts. The (nonDM+nonSepsis) class had the tightest glycemic control among other classes for cohort A and cohort B. There was a significant difference in BG level and glucose intake between cohort A and cohort B, also between sepsis and non-sepsis of non-DM for both cohorts. Cohort B (nonDM+nonSepsis) had the highest BG percentage within the target range (74.31%) and the lowest percentage for hyperglycemia (18.78%), indicating proper control can be achieved within the non-DM and non-sepsis patients. In contrast, Cohort A (nonDM+nonSepsis) had the highest percentage of severe hypoglycemia (0.12%) and a relatively high percentage of severe hyperglycemia (41.55%). This explains that the lower insulin sensitivity profiles of cohort A are among the significant factor contributing to its unsatisfactory performance. Thus, insulin sensitivity, patient variability, diabetes and sepsis status play an essential role in the success of any glycemic control protocol.

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