ORIGINAL ARTICLE

Nutritional Characteristics and Clinical Outcomes of Critically Ill Patients with and without Diabetes Mellitus: A Single-Center Prospective Observational Study in Malaysia

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ABSTRACT

Introduction: This study aimed to compare the nutritional characteristics and clinical outcomes among critically ill patients with diabetes (DM) and without diabetes (WDM). **Methods:** Mechanically ventilated, critically ill patients who were admitted into the intensive care unit (ICU) within 48 hours and remained in ICU ≥72 hours were prospectively recruited and followed for up to 12 days. They were stratified to DM or WDM, depending on their diabetes status at ICU admission and comparison were made for nutritional characteristics and clinical outcomes including 60-day mortality. **Results:** A total of 154 patients were included with 73 (47.4%) DM patients. In comparison to WDM, patients with DM were older, more severely ill, had higher nutritional risk and body mass index, presented with a higher blood glucose level, and required more insulin. DM was fed relatively earlier but had lower energy adequacy. They experienced more frequent EN interruption. Both groups had comparable ICU and hospital stay, ventilation support duration and mortality. In multivariable logistic regression, no association was found between diabetes status and for ICU and hospital mortality. However, There was a trend towards an increase in 60-day mortality in DM patients (Odds Ratio: 2.220, 95% Confidence Interval: 0.764-6.452; p=0.143). **Conclusion:** Critically ill patients with DM had higher nutritional risks, were fed relatively earlier, but with frequent EN interruption leading to lower energy adequacy than patients WDM. Diabetes status does not affect clinical outcomes.

Keywords: Diabetes, Critical care nutrition, Mortality

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INTRODUCTION

Approximately one in six adults (16.6%) in Malaysia had diabetes, a rate that is relatively higher than the global prevalence (8.8%) (1). It then comes as no surprise to observe that diabetes-related complications were among the top 10 most common diagnosis leading to ICU admission (2). Nonetheless, data related to nutritional characteristics and clinical outcomes among critically ill patients with diabetes are scarce.

In non-critically ill patients, lifestyle management including medical nutrition therapy is one of the fundamentals aspects of diabetes care to achieve optimal glycemic control (3,4). On the other hand, patients who are critically ill and had diabetes would require insulin therapy to achieve optimal glycemic control, as the evidence for the use of carbohydrate-restricted formula is still limited (5,6). Nevertheless, overfeeding should be avoided to prevent hyperglycemia (7).

Several large observational studies explored whether diabetes affects clinical outcomes in critically ill patients, but the findings were inconsistence (8-12). These studies found that the presence of diabetes is either protective (8,9), harmful (10), or does not affect clinical outcomes (11,12). This association might be modified by glycemic control including hyperglycemia (11-13), hypoglycemia (8,14) and glycemic variability (8,14,15). In terms of mortality rate, a meta-analysis reported no association between ICU mortality and diabetes status despite the small increase in hospital mortality (16). This analysis observed the mortality was more pronounced among those patients undergoing cardiac surgery (16).

Although nutrition impacts clinical outcomes, limited study compares nutritional characteristics such as timing of initiation of enteral nutrition (EN), energy and protein adequacy and reasons for EN interruption in patients with and without diabetes in ICU setting. (17, 18) Therefore, we primarily aimed to compare the nutritional characteristics (descriptively) between critically ill patients with and without diabetes at ICU admission. Furthermore, clinical outcomes between diabetic status at ICU admission will also be explored. We hypothesized that patients with diabetes have higher nutritional risk and mortality but lower nutrition provision than critically ill patients without diabetes. Our results will assist in understanding the impact of diabetes in critical care nutrition.

MATERIALS AND METHODS

This is a secondary analysis of a prospective observational study investigated the relationship between nutritional adequacy and 60-day mortality (19). The sample size of the original study was 152 patients, which were calculated by assuming a maximum reduction of 40% in 60-day mortality among patients who were fed at least 2/3 of the prescribed amount of energy (19). This study was conducted from April 2015 to April 2016 in a general ICU with 14 beds at a selected government hospital in Malaysia. In this secondary analysis, we stratified the patients according to their diabetes status at ICU admission. A comparison was made for nutritional characteristics and clinical outcomes including the 60-day mortality. This study does not differentiate between types of diabetes. A critically ill patient aged >18 years old who was mechanical ventilated within 48 hours of ICU admission and remained in ICU for >72 hours were included in this study. This study was approved by National Medical Research and Ethics Committee (NMRR-14-1600-23639).

Measurements

The study obtained data from medical record. The data included age (years), sex, race, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, comorbidities and hospital admission category (medical or surgical). APACHE II is used to classify diseases severity with a score ranging from 0 to 71. The higher the score, the higher the risk of mortality (20). SOFA determines the magnitude of organ failure with a score ranging from 0 to 24. The higher the score, the greater the magnitude of organ failure (21). Diagnosis of diabetes was based on medical record and patients were categorized as having diabetes (DM) or without diabetes (WDM).

Nutritional characteristics such as nutritional risk status (as measured by the modified-NUTRIC score), feeding route, feeding mode and feeding process (time to feeding, duration of EN interruption) were also obtained. On a scale of 0 to 9, patients with a modified-NUTRIC score >5 were categorised as a high nutritional risk while ≤5 as a low nutritional risk (18). Patients were followed prospectively in the ICU until died or discharged, for a maximum of 12 days. Daily data collection for nutritional adequacy, duration and reason of EN interruption, morning blood glucose level (reading nearest to time 0800, if 2 measurements are equidistant to 0800, the highest blood glucose reading was recorded), number of days with hypoglycaemia episode (defined as blood glucose level <3.5 mmol/L) and insulin infusion were obtained (19). Energy and protein requirement was calculated based on the 2009 Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient (22). The equations used for the calculation for adequacy of energy and protein intakes were as follows:

$$\text{Energy adequacy} = \frac{\text{Sum of \% of energy received each day}}{\text{Total number of evaluable nutrition days}}$$

$$\text{Protein adequacy} = \frac{\text{Sum of \% of protein received each day}}{\text{Total number of evaluable nutrition days}}$$

where evaluable days were defined as the length of ICU follow-up for a maximum period of 12 days, before patients progressed to permanent and exclusive oral intake. One evaluable nutrition day started at 0000 h and ended at 2359 h of calendar clock (19).

Reasons for EN interruption consisted of four categories based on previous study (23). These include 1) procedural-related (endotracheal tube management, radiological procedures, operating room procedures, bedside procedures and feeding-tube related problem), 2) intolerance to EN which was further subdivided into feeding-related intolerance (diarrhea, increased gastric residual volume, abdominal distension, vomiting and regurgitation) and illness-related intolerance (hemodynamic instability and gastrointestinal bleeding), 3) potentially avoidable reasons (cancelling a planned procedures after feeding withhold, discontinuation of feeding due to inappropriate reasons) and 4) unknown reasons (no reason for EN interruption was documented). The mortality status at day 60 was collected from the hospital record.

Statistical Analysis

All the analysis was done using version 22 of IBM SPSS Statistics. Two-tail $p<0.05$ was considered significant while $p<0.20$ was considered a trend. The normality of the data was tested using the Kolmogorov-Smirnov test and verified by visual inspection of histogram. Continuous data in mean ± standard deviation or median (q1-q3) were reported, as appropriate. Categorical data were presented in count and percentage Patients were stratified into two groups based on their diabetes status upon ICU admission and comparison between groups were made using independent t-test for continuous data and a chi-square test for categorical data. The association between diabetes status (DM vs WDM) and 60-day mortality was determined using multiple logistic regression. Two logistic models were generated i.e. unadjusted and after the adjustment for baseline dissimilarities.

RESULTS

A total of 154 patients were included with 73 patients (47.4%) had a diagnosis of DM. As compared to WDM, patients with DM were older (58.6 vs 44.7 years; p<0.001), mostly admitted due to medical reasons (86.3% vs 69.1%; p=0.011), presented with higher disease severity score (29.0 vs 24.9; p=0.001), more number of comorbidities (3 vs 1; p<0.001), had higher nutrition risk (6.6 vs 4.8, p= 0.000) and higher body mass index (27.65 vs 25.51 kg m^{-2}; p=0.046) (Table I).

Table I: Baseline Characteristics

	Total	Non-diabetic	Diabetic	p-value
N	154	81	73	
Age, years	51.29±15.73	44.74±15.65	58.56±12.34	<0.001
Gender				0.160
Male	83 (53.9)	48 (59.3)	35 (47.9)	
Female	71 (46.1)	33 (40.7)	38 (52.1)	
Race				0.069
Malay	87 (56.5)	51 (63.0)	36 (49.3)	
Chinese	24 (15.6)	8 (9.9)	16 (21.9)	
Indian	28 (18.2)	12 (14.8)	16 (21.9)	
Others	15 (9.7)	10 (12.3)	5 (6.8)	
Admission Category				0.011
Medical	119 (77.3)	56 (69.1)	63 (86.3)	
Surgical	35 (22.7)	25 (30.9)	10 (13.7)	
APACHE II	26.86±7.35	24.94±7.63	28.99±6.43	0.001
SOFA	12.39±3.66	12.06±4.02	12.75±3.21	0.243
Number of Comorbidity	2.00 (1.00-3.00)	1.00 (0.00-2.00)	3.00 (2.50-4.00)	<0.001
NUTRIC	5.65±1.93	4.77±1.88	6.63±1.45	<0.001
NUTRIC category				<0.001
Low risk	68 (44.2)	55 (67.9)	13 (17.8)	
High risk	86 (55.8)	26 (32.1)	60 (82.8)	
Underlying disease				
Hypertension	88 (57.1)	25 (30.9)	63 (86.3)	<0.001
Renal disease	40 (26.0)	14 (17.3)	26 (35.6)	0.010
Heart disease	29 (18.8)	13 (16.0)	16 (21.9)	0.352
Anthropometric Data				
Weight, kg	70.89±18.30	68.87±18.46	73.14±17.97	0.148
Height, m	1.64±1.63	1.64±0.08	1.63±0.09	0.183
BMI, kg m^{-2}	26.52±25.25	25.51±6.81	27.65±6.33	0.046
<18.50	13 (8.4)	9 (11.1)	4 (5.5)	0.112
18.50-29.99	103 (66.9)	57 (70.4)	46 (63.0)	
≥ 30.00	38 (24.7)	15 (18.5)	23 (31.5)	
Glycaemic control				
Morning blood glucose, mmol/L[a]	8.12±1.63	7.35±1.30	8.98±1.53	<0.001
Insulin, unit	15.33±20.35	5.78±10.24	25.93±23.38	<0.001
Days with Hypo-glycaemia[b]	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.901

APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment, NUTRIC: Nutrition risk in the critically ill, BMI: Body mass index
[a]Blood glucose reading nearest to time 0800, if 2 measurements are equidistant to 0800, the highest blood glucose reading was recorded
[b]Hypoglycemia was defined as blood glucose level <3.5 mmol/L

The average morning blood glucose level was higher in DM than WDM (8.98 vs 7.35 mmol/L; p<0.001). Hence, significantly more insulin was required (25.93 vs 5.78 unit; p<0.001). There was no difference in days with hypoglycemia between groups (Table I).

In terms of nutrition, there was a trend towards more EN usage among DM (94.5% vs 80.0%; p=0.019). DM were fed relatively earlier (9 vs 14 h; p=0.177) but they had greater EN interruption (28 vs 21 hr; p=0.020), resulting in significantly lower energy adequacy (60.63% vs 68.06%; p= 0.030) and trends towards lower protein adequacy (54.04% vs 58.67%; p=0.165). Both cumulative 12-day energy and protein balance were significantly lower in DM (-4639.6 kcal vs -3314.3 kcal; p=0.002 and -271.1 vs -221.8g; p=0.023, respectively). The reasons for EN interruption was further investigated. There was a trend towards more frequent EN interruption among DM due to procedures (16 h vs 12 h; p=0.156) and illness-related intolerance (37.5 h vs 19.0 hr; p=0.208). Meanwhile, patients WDM had a trend towards more interruption due to feeding-related intolerance (8.50 vs 5.00 hr; p=0.186) (Table II).

Table II: Nutritional Characteristics

	Total	Non-diabetic	Diabetic	p-value
N	154	81	73	
Evaluable nutrition day	10.00 (7.00-12.00)	9.00 (6.00-12.00)	10.00 (7.00-12.00)	0.366
Feeding process				
Time to first feeding (EN or PN, h	11.50 (4.00-21.25)	14.00 (4.00-27.50)	9.00 (4.50-18.50)	0.177
Time to first EN, h	11.00 (4.00-21.50)	13.50 (4.00-28.75)	9.00 (4.50-19.50)	0.190
Days with motility agent	2.00 (0.00-5.00)	2.00 (0.00-5.00)	1.00 (0.00-4.00)	0.178
EN interruption, h (n=151)*	24.00 (13.00-38.00)	21.00 (11.75-35.00)	28.00 (15.00-41.00)	0.020
Procedural-related (n=120)[a]	14.50 (8.00-24.00)	12.00 (7.00-22.50)	16.00 (9.00-25.00)	0.156
Feeding-intolerance (n=23)[b]	5.00 (3.00-11.00)	8.50 (3.00-14.75)	5.00 (3.00-6.00)	0.186
Illness-intolerance (n=24)[c]	28.50 (11.50-39.00)	19.00 (13.25-29.75)	37.50 (5.75-53.25)	0.208
Potentially Avoidable reason (n=71)[d]	12.00 (6.00-20.00)	12.00 (6.00-18.25)	12.00 (6.00-21.00)	0.903
Unknown (n=42)[e]	3.00 (3.00-6.25)	3.00 (2.00-6.00)	3.00 (3.00-7.00)	0.547
Initial EN feeding mode				0.567
Bolus	89 (60.1)	44 (57.9)	45 (62.5)	
Cyclic[f]	59 (39.9)	32 (42.1)	27 (37.5)	
Feeding Route				0.019
Total EN	133 (86.9)	64 (80.0)	69 (94.5)	
Total PN	4 (2.6)	4 (5.0)	0	
EN+PN	16 (10.5)	12 (15.0)	4 (5.5)	
Nutrition Delivered				
Energy Intake, kcal	969.85 ± 326.79	1026.63 ± 354.40	906.85 ± 282.37	0.023
Protein Intake, g	40.60 ± 14.71	42.23 ± 15.93	38.79 ± 13.09	0.148
Energy adequacy, %	64.54 ± 21.51	68.06 ± 23.89	60.63 ± 17.89	0.030
Protein adequacy, %	56.47 ± 20.63	58.67 ± 22.73	54.03 ± 17.87	0.165
12-d Energy balance, kcal	-3942.49 ± 2726.25	-3314.27 ± 2943.12	-4639.56 ± 2287.55	0.002
12-d Protein balance, g	-245.13 ± 135.08	-221.76 ± 144.66	-271.07 ± 119.28	0.023

h: hour, EN: Enteral nutrition, PN: Parenteral nutrition, g: gram, d: day, kcal: kilocalorie
*Each patient can have more than two type of EN interruption
[a]Respiratory, radiological, operating room, bedside and feeding-tube related procedures
[b]Elevated gastric residual volume, abdominal distension, vomiting or regurgitation and diarrhea
[c]Gastrointestinal bleeding, hemodynamic instability
[d]Planned procedures not executed after fasting, inappropriate (not evidence based) reasons
[e]Reason for interruption not documented in the medical records
[f]Cyclic feeding in our setting is feeding continuously by using a feeding pump for 4 hours and rest for 1 hour

Lengths of ICU and hospital stay, duration of mechanical ventilation and ICU mortality were comparable between groups (Table III). However, hospital and 60-day mortality were higher in DM as compared to WDM patients (52.1% vs 33.3%; p=0.019 and 56.2% vs 34.6%; p=0.007, respectively). This association remained in the unadjusted logistic model.

Table III: Clinical Outcomes

	Total	Non-diabetic	Diabetic	p-value
N	154	81	73	
ICU LOS, day	9.41 (6.42-15.46)	9.44 (5.91-17.17)	9.14 (7.10-15.00)	0.597
Hospital LOS, day	19.22 (12.64-36.66)	19.21 (13.03-36.48)	19.85 (12.42-36.84)	0.817
Duration of MV, day	8.64 (5.15-15.00)	7.76 (4.88-15.32)	8.94 (5.59-14.80)	0.587
Mortality				
ICU mortality	43 (27.9)	19 (23.5)	24 (32.9)	0.193
Hospital mortality	65 (42.2)	27 (33.3)	38 (52.1)	0.019
60-day mortality	69 (44.8)	28 (34.6)	41 (56.2)	0.007

ICU: Intensive care unit, LOS: Length of stay, MV: Mechanical ventilation

Adjustments in the logistic regression analysis were made for baseline dissimilarities (age, APACHE II, number of co-morbidity, BMI, admission category, hypertension and renal disease), mean 12-day morning blood glucose and energy adequacy (%). After controlling for these variables, no relationship was shown between diabetes status and ICU mortality (Adj OR [adjusted odds ratio] 1.155, 95% CI [confidence interval] 0.378-3.529; p=0.800) as well as between diabetes status and hospital mortality (Adj OR 1.717, 95% CI 0.612-4.815; p=0.304). Nevertheless, a trend towards higher 60-day mortality (Adj OR 2.220, 95% CI 0.764-6.452; p=0.143) among DM was still evident (Table IV).

Table IV: The Association Between Diabetes Status and Mortality

	Unadjusted Model		Adjusted Model[a]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
ICU Mortality	1.598 (0.787-3.247)	0.195	1.155 (0.378-3.529)	0.800
Hospital mortality	2.171 (1.132-4.165)	0.020	1.717 (0.612-4.815)	0.304
60-day mortality	2.425 (1.265-4.649)	0.008	2.220 (0.764-6.452)	0.143

ICU: Intensive care unit, OR: Odds ratio, CI: Confidence interval
[a]Adjusted for age, APACHE II, number of co-morbidity, body mass index, admission category, hypertension and renal disease, mean 12-day morning blood glucose and energy adequacy (%)

DISCUSSION

This study showed that nearly half (47.4%) of critically ill patients admitted to our ICU had diabetes. Compared with other studies (10, 14), about 15.7% and 15.9% of the total subjects, respectively, were having diabetes. Our prevalence is almost three times higher than these studies. Such high prevalence is expected as the Asian generally are more susceptible to DM and that our population has a prevalence of DM that is twice the world prevalence. (1)

Compared with WDM, DM patients were significantly older and presented with higher disease severity, number of comorbidities, nutritional risk and BMI. They also had significantly higher average 12-day morning blood glucose and therefore, required more insulin infusion. These differences in baseline characteristics are like other studies (10,14). It is noteworthy to mention that our average blood glucose level is in line with the optimal blood glucose level as recommended by critical care nutrition guidelines (7-9 mmol/L) (5).

For nutritional characteristics, although DM patients were fed relatively earlier than WDM, energy and protein adequacy were still lower among DM, most probably due to more frequent EN interruption. We demonstrated that EN was interrupted more frequently among DM due to procedures and illness-related intolerance. This is most probably due to the higher disease severity and several comorbidities presented by DM patients. On the other hand, WDM had more episodes of EN interruption due to feeding-related intolerance. The observation of better gastric tolerance among DM is in line with the other studies. They identified patients who are critically ill and have diabetes experienced regular or even rapid gastric emptying than non-diabetes patients (24). Overall, these findings suggest that more attention should be paid to optimizing nutritional intake among DM patients such as minimizing fasting time for procedures. Furthermore, prophylactic strategies such as initiate feeding with a peptide formula can be considered for patients WDM to minimize feeding-intolerance, although more evidence are needed to prove the efficacy of such approach (25).

After adjusting for baseline dissimilarities, our results showed no association between diabetes status and ICU and hospital mortality. However, there was a trend towards increased 60-day mortality among DM patients. The absence of an association between diabetes status and mortality is consistent with other studies (11,12) and meta-analysis (16). Stegenga et al (11) showed that diabetes status in patients with severe sepsis does not increase mortality at 28 and 90 days. Similarly, Van Vught et al (12) demonstrated that diabetes status per se did not impact crude 30-day mortality. However, hyperglycemia (>11.1 mmol/L) at ICU admission increased the risk of mortality not only in patients with DM but also in patients WDM (12). In a meta-analysis, DM was not associated with an increased in mortality except among patients underwent cardiac surgery (16). The worse outcome among cardiac surgical patients is probably due to the serious cardiac-related conditions as well as a higher rate of sternal wound infection among these patients population (16).

This study has several limitation. The generalizability of the study is limited as this is a single-centre study with small sample size. On the other hand, as diabetes status was determined at ICU admission, there is a risk that we misclassified patients with undiagnosed DM to the WDM group. However, we believe that such error is minimal as our baseline characteristics shown that DM group were more severely ill and required more insulin for glycemic control than WDM group. For the association between diabetes status and mortality, our study is limited by other residual confounders. Such association may be influenced by factors such as hyperglycemia (11-13), hypoglycemia (8,14) and/or glycemic variability (8,14,15). In our study, the days of hypoglycemia between DM and WDM were comparable, and we have adjusted for the differences in blood glucose levels between groups in our logistic model. The effect of glycemic variability, however, was not investigated. Furthermore, we also did not adjust for the impact of medicines that may affect the outcome of DM patients who are critically ill, such as statins, inhibitors of the renin-angiotensin system, HMG-CoA reductase inhibitors, proliferator-activated receptor gamma agonists, and aspirin (10,26). In addition, the complete picture of glycemic control in the ICU may not be captured as only morning blood glucose level was recorded. However, this reading and the total insulin unit recorded may provide a rough estimate of glycemic control. It is recommended to record the highest and lowest daily blood glucose level for future study. Lastly, this study is not powered for mortality, the association between diabetes status and mortality is only exploratory and hypothesis-generating.

Despite the study's limitation, this study provides important data about diabetes status and compared the nutritional characteristics between DM and WDM among critically ill patients in Malaysia. Also, we have adjusted for the effect of nutritional variables for the association between diabetes status and mortality, which was shown to affect mortality among critically ill patients (27).

CONCLUSION

In a single-center ICU in Malaysia, the prevalence of diabetes among critically ill patients with mechanical ventilation is 47.4%. DM had lower energy adequacy. This may be due to the more frequent EN interruption due to procedures or illness-related intolerance among DM. After adjustment for baseline dissimilarities, we found that diabetes status was not associated with ICU and hospital mortality. However, a trend towards increased 60-day mortality among DM was observed, which warrants further investigation.

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