Original Article

Outcome of glycemic control in critically ill patients receiving enteral formulas

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Background and Objectives: Stress hyperglycemia is a common condition in critically ill patients. Inappropriate nutritional supplementation may worsen blood glucose control in these patients. The present study aimed to investigate the outcome of blood glucose control status when using various enteral formulas. **Methods and Study Design:** This retrospective study was conducted at the intensive care unit of a tertiary medical center in central Taiwan. Patients meeting the following inclusion criteria were enrolled in the study: age ≥20 years, respiratory failure requiring mechanical ventilation, and two consecutive blood glucose concentration measurements of ≥180 mg/dL. Demographic data, blood glucose samples, and hospital mortality were collected for analysis. **Results:** A total of 4,604 blood glucose samples from 48 patients were analyzed. Results demonstrated no significant difference in mortality rate or blood glucose control between patients fed semi-elemental formulas and those fed polymer formulas. Serum HbA1C of <7.5% was a risk factor for hospital mortality (OR: 0.18, 95% CI: 0.04–0.89). Enteral formulas containing less carbohydrate were associated with better blood glucose control. **Conclusions:** No significant difference in the outcome of blood glucose control was observed between patients fed semi-elemental formula and those fed polymer formula. To achieve better blood glucose control in critically ill patients, formulas with lower carbohydrate content should be considered.

Key Words: critically ill patients, hyperglycemia, semi-elemental formula, polymer formula, enteral nutrition

INTRODUCTION

Hyperglycemia is a common condition in critically ill patients.[1-3] Approximately 60% of critically ill patients without a history of diabetes experience hyperglycemia during intensive care unit (ICU) stay.[4] Insulin resistance is the main cause of hyperglycemia and >80% of critically ill patients develop insulin resistance.[5] Cytokine activity, endocrine abnormality, and inappropriate nutritional supplementation also impair glucose control in ICU patients.[6]

In addition to hyperglycemia, hypoglycemia and high glucose variability (GV) also result in poor outcomes.[4,7-10] Moreover, dysglycemia-related poor outcomes appear similar between patients with diabetes mellitus[11] and those without.[4,7,11,12] Administration of polymer formula rather than semi-elemental formula is recommended, except for patients with diarrhea, by the American Society for Parenteral and Enteral Nutrition and the European Society of Intensive Care Medicine guidelines.[13,14] How polymer or semi-elemental formula affects blood glucose control in patients is unknown. Macronutrients in nutritional supplements and parenteral nutrition are important for blood glucose control in critically ill patients.[6] Lowering the carbohydrate content results in better blood glucose control in ambulatory patients with diabetes.[15,16] In critically ill patients, low-carbohydrate formula has also been demonstrated to achieve superior results for blood glucose control.[17,18] A prospective study conducted in Australia revealed that a low-carbohydrate enteral formula administered to hyperglycemic patients within the first 48 h of ICU admission resulted in reduced use of insulin and low GV.[19]

Hyperglycemia can occur in critically ill patients any time during their hospital stay, especially those in the ICU. However, it remains unclear whether the semi-elemental or polymer formula provides superior blood glucose control. Further, it is unclear whether different semi-elemental formulas yield different clinical outcomes.

To answer these questions, we conducted a retrospective study to determine the effects of various enteral formulas on blood glucose control and clinical outcomes in critically ill patients.

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METHODS

Medical charts of all participants were retrospectively reviewed. Data recorded from September 2017 to July 2018 at the ICU of a tertiary medical center in central Taiwan were analyzed. The study was approved by the institutional review board of the hospital (IRB no: CE19350A). Informed consent was waived because data in this study were retrospectively obtained from medical charts. Inclusion criteria for participants were as follows: age ≥20 years old, respiratory failure requiring mechanical ventilation, and two consecutive blood glucose measurements of ≥180 mg/dL for samples obtained through finger sticks during the ICU stay. The physician-in-charge agreed to control blood glucose by study protocol. Exclusion criteria were as follows: any nil per os orders during ICU stay, ICU stay of <72 h, and administration of hospice care during ICU stay. All participants received either enteral or parenteral nutritional support in accordance with the physician's clinical decision (Supplementary Figure 1 demonstrates the study flow).

Insulin resistance is a common major concern in critically ill patients. Our study protocol was based on the Yale-New Haven Hospital intensive insulin protocol, with modifications.[20] In accordance with the modified Yale-New Haven Hospital intensive insulin protocol, the insulin infusion dosage for this study was determined based on previous and current blood glucose concentrations.[21] Accordingly, we collected data on changes in blood glucose concentration during each adjustment of the insulin infusion rate to reflect insulin responsiveness. Finger stick blood glucose monitoring was used to measure capillary blood glucose concentrations. Sampling intervals were adjusted to 30 min from 4 h according to the protocol instructions. Diet prescriptions during the study period were two types of semi-elemental enteral formulas (A and B) and one polymer formula. The choice of formula prescription was decided by the dietitian. The carbohydrate contents of formulas A and B were 49% and 65%, respectively, whereas that of the polymer formula was 45%-57%. For patients in the ICU, a volume-based feeding protocol (25 kcal/kg/d) was used.

Basic demographic data, such as age, sex, comorbidities, daily energy intake (enteral and parenteral nutrition), and insulin dosage and formula were collected for each patient.

Outcome measurements

Outcome measurements were as follows: hospital mortality, days of ventilator dependence, days of ICU stay, days of hospital stay, GV, and insulin responsiveness. Standard deviation (SD) and the percentage coefficient of variation (CV) for glucose (%CV = [(SD of glucose)/(mean glucose concentration)] × 100) were used to represent GV.[22-24] According to the intensive insulin protocol, patients with the following three blood glucose intervals require intervention: (a) 120-159 mg/dL, (b) 160-199 mg/dL, and (c) ≥200 mg/dL. In addition to the general outcomes for individual patients, we also compared the blood glucose outcomes across different formulas. Ideal blood glucose concentration is within the range of 140-180 mg/dL, whereas hyperglycemia is defined as a concentration of >180 mg/dL. The calculation of insulin responsiveness came from differences between two consecutive blood glucose readings by the intervention of blood glucose protocol.

Statistical analyses

All data were analyzed using the SPSS (version 22.0; International Business Machines Corp, Armonk, NY, USA). Continuous variables were expressed in mean and SD, and differences were assessed using the Mann–Whitney U and Kruskal–Wallis tests. Categorical variables were expressed in number and percentage, and differences were assessed using the chi-square and Fisher's exact tests. Post hoc analysis was conducted using the Dunn–Bonferroni post hoc test. Multivariate logistic regression was used to estimate the ORs and 95% CIs for hospital mortality. All tests were performed according to two-sided tests, with a p value of <0.05 considered statistically significant.

RESULTS

In total, 48 patients were enrolled in the study, of whom 38 (79.2%) had diabetes. The overall hospital mortality rate was 33.3%. No significant difference in any of the following was evident between patients who survived and those who died: age, sex, BMI, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, average daily energy intake, comorbidities, insulin dosage, and blood glucose concentrations. Patients with an HbA1C measure ≥7.5% had a higher survival rate than those with an HbA1C measure of <7.5% (Table 1). According to the multivariate analysis, an HbA1C measure of <7.5% (OR: 0.18, 95% CI: 0.04–0.89) was a risk factor for hospital mortality after adjusting for age, sex, and APACHE II score (Table 2) We also compared the characteristics of patients following enteral formula supplementation. The SOFA score was higher in patients receiving semi-elemental formula; these patients consumed less daily calories (Table 3). No significant difference was observed in outcome measurements such as hospital mortality, days of hospital stay, mean blood glucose concentration, and GV across the groups receiving different enteral formulas (Table 3).

We evaluated two semi-elemental formulas (A and B) and one polymer formula in this study. To analyze the blood glucose concentration under the administration of each specific enteral formula more precisely, we further compared data of the patients receiving semi-elemental formula A, semi-elemental formula B, and polymer formula. Results revealed significant differences in mean blood glucose concentration, number of ideal blood glucose readings (concentration: 140–180 mg/dL), and number of hyperglycemic readings (concentration: >180 mg/dL; Table 4). In the post hoc analysis, semi-elemental formula A was associated with lower mean blood glucose concentration (p<0.001), more ideal blood glucose readings (p<0.01), and fewer hyperglycemic readings (p<0.001) compared with semi-elemental formula B. Furthermore, compared with the polymer formula, semi-elemental formula A was associated with lower mean blood glucose concentration (p<0.001) and fewer hyperglycemic readings (p<0.01). Semi-elemental formula A was associated with lower blood glucose elevation in patients administered a specific amount of insulin within the blood glucose range of 120–159 mg/dL compared with patients receiving

Table 1. Patient demographic characteristics (n=48)

Variables	Survivor (n=32)		Non-survivor (n=16)		*p* value
	Mean or n	SD or %	Mean or n	SD or %	
Age	70.0	12.8	62.3	14.7	0.076
Sex-Men† (n, %)	12	37.5	11	68.6	0.082
BMI	25.4	4.90	26.9	4.93	0.265
Apache II	26.9	5.86	29.6	5.32	0.107
SOFA score	9.53	3.80	10.4	3.20	0.404
HbA1C ≥7.5%† (n, %)	21	65.6	4	25	0.019*
Albumin	3.01	0.59	2.89	0.63	0.319
Average daily energy intake (PN+ EN) (kcal/day)	1393	318	1460	330	0.347
Average daily energy intake (EN) (kcal/day)	1350	330	1362	370	0.726
Average daily protein intake (PN+EN) (g/day)	57.6	13.5	55.6	17.4	0.662
Average daily protein intake (EN) (g /day)	57.1	13.7	55.6	17.4	0.726
Average daily fat intake (PN+EN) (g /day)	50.7	18.4	56.1	21.5	0.347
Average daily fat intake (EN) (g /day)	50.4	18.1	54.1	21.9	0.585
Average daily carbohydrates intake (PN+EN) (g/day)	183	38.6	190	29.9	0.347
Average daily carbohydrates intake (EN) (g /day)	171	40.3	166	39.2	0.743
Sepsis† (n, %)	12	37.5	5	31.3	0.915
ARDS† (n, %)	1	3.13	2	12.5	0.254
Formula† (n, %)					1.000
Semi-elemental formula	14	43.8	7	43.8	
Polymer formula	18	56.3	9	56.3	
Comorbidity† (n, %)					
Diabetes mellitus	26	81.3	12	75.0	0.712
Hypertension	5	15.7	2	12.5	1.000
COPD	2	6.25	0	0.00	0.546
Congestive heart failure	3	9.38	1	6.25	1.000
Immunocompromised host	3	9.38	1	6.25	1.000
Liver cirrhosis	2	6.25	3	18.8	0.316
Hemodialysis	4	12.5	6	37.5	0.064
Length of hospital stay (Day)	49.7	47.6	39.4	29.4	0.431
Length of ICU stay (Day)	20.3	17.3	22.7	13.9	0.341
Length of ventilator dependency (Day)	22.3	27.9	25.9	15.1	0.067
Insulin dosage (μ/hr)	4.43	2.82	5.39	3.25	0.227
Blood glucose					
Mean glucose (mg/dL)	182	28.8	189	36.3	0.930
Glycemic variation (SD)	69.3	27.0	72.8	26.1	0.600
Glycemic variation (CV)	37.3	11.1	37.8	8.19	0.555

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA Score: Sequential Organ Failure Assessment Score; PN: parenteral nutrition; EN: enteral nutrition; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease.
Continuous data are expressed as mean and SD; Categorical data are expressed as number and percentage
†Chi-square test. Fisher's exact test. Mann–Whitney U test.
*$p<0.05$.

Table 2. Adjusted ORs of hospital mortality

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	0.96	(0.91-1.00)	0.074	0.95	(0.90-1.01)	0.089
Sex (man vs women)	3.67	(1.02-13.1)	0.046*	3.95	(0.86-18.2)	0.078
Apache II	1.10	(0.97-1.24)	0.132	1.11	(0.95-1.29)	0.187
HbA1C (≥7.5% vs <7.5%)	0.17	(0.05-0.67)	0.011*	0.18	(0.04-0.89)	0.036*

Logistic regression. *$p<0.05$.

the polymer formula in the post hoc analysis ($p<0.05$). Semi-elemental formula A was similarly superior in blood glucose control in patients with diabetes (Supplementary table 1). The insulin responsiveness within the blood glucose range of 120–159 mg/dL was higher in patients receiving semi-elemental formula A than in those receiving the polymer formula in the post hoc analysis ($p<0.05$). No patients without diabetes mellitus administered semi-elemental formula A. The polymer formula had a lower mean blood glucose concentration or fewer hyperglycemic readings compared with those administered semi-elemental formula B. No insulin responsiveness difference was observed between the groups administered semi-elemental formula B and that administered the polymer formula (Supplementary table 2).

DISCUSSION

Acute hyperglycemia often occurs in critically ill patients,

Table 3. Patient demographic characteristics presented according to groups receiving different formulas (n=48)

Variables	Semi-elemental (n=21)		Polymer (n=27)		*p* value
	Mean or n	SD or %	Mean or n	SD or %	
Age	65.5	13.3	68.9	14.3	0.339
Sex-Men† (n, %)	8	38.1	15	55.6	0.363
BMI	25.5	3.62	26.2	5.75	0.876
Apache II	28.5	6.39	27.2	5.30	0.762
SOFA score	11.0	3.37	8.96	3.60	0.033*
HbA1C ≥7.5%† (n, %)	10	47.6	15	55.6	0.799
Albumin	2.93	.58	3.01	0.62	0.755
Average daily energy intake (PN+ EN) (kcal/day)	1269	361	1529	232	0.006**
Average daily energy intake (EN) (kcal/day)	1199	378	1474	253	0.005**
Average daily protein intake (PN+EN) (g /day)	50.5	15.3	61.9	12.4	0.014*
Average daily protein intake (EN) (g /day)	50.4	15.2	61.5	12.9	0.017*
Average daily fat intake (PN+EN) (g /day)	42.2	21.2	60.4	13.7	0.002**
Average daily fat intake (EN) (g /day)	41.6	20.9	59.4	13.9	0.001**
Average daily carbohydrates intake (PN+EN) (g /day)	178	36.7	190	34.7	0.424
Average daily carbohydrates intake (EN) (g /day)	159	42.5	178	35.8	0.194
Sepsis† (n, %)	9	42.9	8	29.6	0.518
ARDS† (n, %)	2	9.52	1	3.70	0.574
Comorbidity† (n, %)					
Diabetes mellitus	17	81.0	21	77.8	1.000
Hypertension	3	14.3	4	14.8	1.000
COPD	0	0	2	7.41	0.497
Congestive heart failure	2	9.52	2	7.41	1.000
Immunocompromised host	3	14.3	1	3.70	0.306
Liver cirrhosis	1	4.76	4	14.8	0.369
Hemodialysis	5	23.8	5	18.5	0.729
Mortality	7	33.3	9	33.3	1.000
Length of hospital stay (Day)	53.3	57.4	40.7	25.1	0.724
Length of ICU stay (Day)	23.6	20.1	19.2	12.3	0.546
Length of ventilator dependency (Day)	25.5	30.6	21.9	18.4	0.851
Insulin dosage (μ/hr)	4.69	3.99	4.80	1.94	0.112
Blood glucose					
Mean glucose (mg/dL)	181	28.2	188	33.6	0.400
Glycemic variation (SD)	70.1	28.4	70.7	25.5	0.701
Glycemic variation (CV%)	37.9	11.0	37.1	9.69	0.925

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA Score: Sequential Organ Failure Assessment Score; PN: parenteral nutrition; EN: enteral nutrition; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease.
Continuous data are expressed as mean or SD; Categorical data are expressed as number and percentage.
†Chi-square test. Fisher's exact test. Mann–Whitney U test.
*p<0.05, **p<0.01.

Table 4. Blood glucose concentration across groups receiving different formulas (n=4,604)

Variables	Semi-elemental A (n=197)		Semi-elemental B (n=459)		Polymer (n=3948)		*p* value
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	
Blood glucose (mg/dL)	179	70.0	221	87.8	192	64.4	<0.001*
BG: 140-180 mg/dL† (n, %)	84	42.6	136	29.6	1481	37.5	0.001**
BG >180 mg/dL† (n, %)	70	35.5	266	58.0	1815	46.0	<0.001**
Insulin responsiveness (mg/dL)	0.09	45.3	-5.27	48.0	0.52	47.1	0.071
120-159	11.4	44.5	18.2	36.3	19.4	44.3	0.032*
160-199	-2.16	23.9	-7.77	31.2	-2.16	40.7	0.221
≥200	-21.3	61.5	-18.3	55.9	-17.4	48.7	0.907

BG: blood glucose.
Categorical data are expressed as number and percentage; Continuous data are expressed as mean or SD.
†Chi-squared test.
*p<0.05, **p<0.01.

and its relationship with mortality is complex. In ICUs, patients without diabetes who develop hyperglycemia have a higher mortality rate than those with diabetes.[9] In patients with well-controlled diabetes, acute hyperglycemia is associated with higher mortality, but not in those with an-HbA1C measure of >7%.[25] In this study, an HbA1C measure of <7.5% was a risk factor for hospital mortality (Table 2). Overly rapid correction of chronic hyperglycemia may be harmful, relative neuroglycopenia might be an explanation.[26] Therefore, a more liberal blood glucose control approach is recommended in patients with a relatively high HbA1C measure for improved clinical outcomes.[27]

The mean blood glucose concentration in our study was slightly higher than 180 mg/dL. Few episodes of severe hypoglycemia (<40 mg/dL) were recorded. Our blood glucose control approach was liberal, which may explain why patients with higher HbA1C measures had better survival rates in our result.

In addition to hyperglycemia and hypoglycemia, higher GV is another potential predictor of poor prognosis.[28] Higher GV is associated with higher mortality.[29-31] Numerous factors such as disease and nutritional status contribute to high GV.[29,30] In the present study, GV did not differ across categories of mortality and feeding formula (Tables 1 and 3). This discrepancy with the literature may be because we collected some blood glucose data only during insulin protocol interventions. Further, the limited body of data likely failed to explain the entire outcome.

The characteristic of the Yale protocol is mainly individualized insulin rate adjustment.[20] Disease severity and insulin responsiveness are heterogeneous among critically ill patients. Each insulin dosage adjustment in the Yale protocol is based on prior and current blood glucose readings. Thus, we assessed insulin responsiveness to discern differences among the formulas. The low frequency of severe hypoglycemic readings under the current insulin protocol is consistent with those reported under the Yale protocol in the literature.[21]

The choice of nutritional therapy for critically ill patients is enteral nutrition, but without a "one size fits all" formula. The choice of formula is based on polymeric nutrients in most cases, and semi-elemental formula is preferred for patients with malabsorption or long-term starvation.[32] Major outcome measurements in our study (i.e., hospital mortality, days of ICU stay, ventilator dependence, and blood glucose control) were similar across all groups (Table 3). Thus, it was to be expected that we would observe lower energy intake and higher disease severity scores in those receiving semi-elemental formulas. These patients tend to be in an unstable condition or an acute disease phase. Although a relatively low mortality rate has been noted after high energy intake in patients with severe illness,[33,34] we did not observe a similar phenomenon in our study, possibly because our data came from different time points during ICU stays. Most studies have analyzed energy intake during the first week after ICU admission.

One study reported that giving low-carbohydrate enteral formula to hyperglycemic patients within the first 48 h after admission is associated with better blood glucose control.[19] In our study, we found no evidence of blood glucose being affected by the two major diet formulas (Table 3). For analysis, therefore, we divided patients receiving semi-elemental formula into two groups, A and B, on the basis of macronutrient distribution. The carbohydrate content was lower in formula A than in formula B. In the post hoc analysis of the three formulas, we found that semi-elemental formula A was associated with increased ideal blood glucose readings and better insulin responsiveness compared with semi-elemental formula B and polymer formula (Table 4). These results are consistent with those reported in the literature.[35,36] The European Society for Clinical Nutrition and Metabolism guidelines also suggest that the adequacy of carbohydrate administration should always be considered for patients in the ICU with hyperglycemia.[35] Some studies have preferred to administer diabetes-specific formulas to achieve superior glucose control.[17,18] Our results revealed that even patients with diabetes attained satisfactory blood glucose control with semi-elemental formula A (Supplementary table 1). This finding was not observed with semi-elemental formula B, regardless of whether the patient had diabetes mellitus or not (Supplementary table 2). Determining the optimal carbohydrate content is a key to achieve ideal blood glucose control rather than depending solely on the choice of diet formula (semi-elemental or polymer formula).

To our knowledge, our present study is the first to compare the effect of semi-elemental and polymer formulas on blood glucose control. The strength of our study is that we collected intensive blood glucose data almost hourly for blood glucose analysis in accordance with a well-documented protocol. In addition to mean blood glucose concentration, the number of ideal blood glucose readings, and the number of hyperglycemic readings, we also included GV as an outcome measurement. This study inevitably has some limitations. First, it was a retrospective study, and we were unable to control many variables. Our present results should be verified with a well-designed prospective study. Second, decision of formula prescriptions depended on patients' clinical status. Disease status is typically time-variant for critically ill patients. We argue that it is useless to prescribe a specific feeding formula without adjusting for the changing disease status. Third, finger stick capillary blood glucose monitoring was used in this study. Arterial blood glucose test may be a superior option for higher precision in future studies. Fourth, the daily energy requirement was simply estimated using a weight-based equation (25 kcal/kg/d) rather than through respiratory quotient or indirect calorimetry. Therefore, real energy needs may have been imprecisely calculated.

Conclusions

No significant differences in blood glucose control and hospital mortality were evident between patients receiving semi-elemental formula and that receiving polymer formula. A serum HbA1C measure of <7.5% was a risk factor for hospital mortality in critically ill patients with liberal blood glucose control. To achieve better blood glucose control in critically ill patients, formulas with lower carbohydrate content should be considered.

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AUTHOR DISCLOSURES

The authors declare no conflicts of interest. This study was supported by Taichung Veterans General Hospital, (TCVGH-1094402B), Taichung, Taiwan.

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Supplementary table 1. Blood glucose concentration among groups receiving different formulas (patients with diabetes mellitus) (n=3,860)

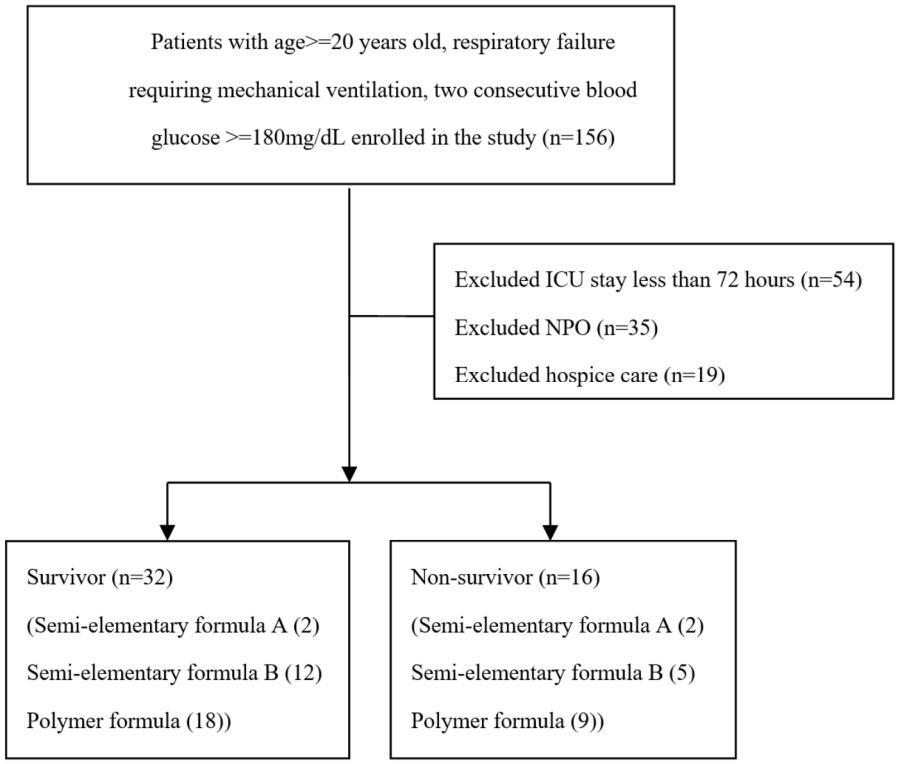
Variables	Semi-elemental A (n=197)		Semi-elemental B (n=327)		Polymer (n=3336)		*p* value
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	
Glucose (mg/dL)	179	70.0	221	76.6	193	65.0	<0.001**
BG: 140-180 mg/dL† (n, %)	84	42.6	89	27.2	1219	36.5	0.001**
BG >180 mg/dL† (n, %)	70	35.5	203	62.1	1583	47.5	<0.001**
Insulin responsiveness (mg/dL)	0.09	45.3	-4.26	42.0	0.38	46.8	0.171
120-159	11.4	44.5	17.9	37.0	19.8	41.9	0.019*
160-199	-2.16	23.9	-6.71	33.1	-1.75	42.0	0.358
≥200	-21.3	61.5	-14.6	44.3	-17.2	48.7	0.847

BG: blood glucose.
Categorical data are expressed as number and percentage; Continuous data are expressed as mean and SD.
†Chi-squared test.
*p<0.05, **p<0.01.

Supplementary table 2. Blood glucose concentration among groups receiving different formulas (patients without diabetes mellitus) (n=744)

Variables	Semi-elemental B (n=132)		Polymer (n=612)		*p* value
	Mean or n	SD or %	Mean or n	SD or %	
Glucose (mg/dL)	222	111	185	60.7	0.015*
BG: 140-180 mg/dL† (n, %)	47	35.6	262	42.8	0.154
BG >180 mg/dL† (n, %)	63	47.7	232	37.9	0.046*
Insulin responsiveness (mg/dL)	-7.78	60.5	1.32	48.7	0.198
120-159	18.6	35.3	17.7	53.1	0.309
160-199	-10.5	26.1	-4.53	31.9	0.418
≥200	-29.5	81.2	-18.5	48.9	0.220

BG: blood glucose.
Categorical data are expressed as number and percentage; Continuous data are expressed as mean and SD.
†Chi-squared test.
*p<0.05.



Supplementary figure 1. Study flow chart.