ORIGINAL ARTICLE

Nutritional Prescription in ICU Patients: Does it Matter?

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Abstract

Background: The nutritional status of the patients before critical illness and nutrition support given during the critical illness play an important role in the recovery. We aimed to evaluate the nutritional prescription and its effect on ICU mortality.

Materials and methods: This was a prospective observational study conducted after institutional ethical committee approval (IEC 94/2018, CTRI/2018/06/014625) in a case-mixed (medical and surgical) ICU. Patients admitted to the ICU were enrolled within 24 hours of admission. The amount of calories and proteins prescribed and received by the patients was collected for 7 days. The primary outcome was ICU mortality.

Results: A total of 100 patients were included. The mean age was 48.63 (16.25) years, and 62% were males. The acute physiology and chronic health evaluation (APACHE II), sequential organ failure assessment (SOFA), and modified Nutric (mNUTRIC) scores were comparable between the two groups. The ICU mortality was 30%. The calorie and protein deficits were comparable between survivors and non-survivors. Among the secondary outcomes, a significant time effect ($p = 0.013$) and interaction effect ($p = 0.004$) were noted for maximum glucose levels. The glucose variability calculated by coefficient of variation (CV) was significantly higher in non-survivors than survivors ($p = 0.031$).

Conclusion: The calorie and protein deficits did not affect ICU mortality. The maximum glucose variability and CV were significant parameters associated with ICU mortality.

Keywords: Calorie deficit, Coefficient of variation, Glucose variability, mNUTRIC score, Nutrition prescription.

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Highlights

This study focused on the effect of nutritional prescription on the ICU mortality.

The prescribed calories and proteins, or deficits in delivered nutrition did not predict the ICU mortality.

We observed glycemic variability [coefficient of variation (CV)] and changes in the maximum glucose levels over 7 days were the predictors of mortality.

Several factors can affect glycemic variability. Hence future research should focus on the effect of these risk factors including nutrition on glycemic variability and ICU mortality.

Introduction

Nutrition plays a vital role in the recovery from critical illness. Patients admitted with critical illness require various interventions like administration of antibiotics, ventilator support, renal replacement therapy, vasopressor support, and surgery in the selected cases. During this critical phase, nutritional status before the illness and the nutritional support received in the ICU can impact ICU mortality.[1,2]

The gold standard for measuring energy expenditure is the indirect calorimetry. With the mixed results from the recent meta-analyses and also due to the lack of availability of this technology in most ICUs, prediction equations are used as a reference for prescribing calories.[3–5]

The nutrition prescription is based on the ESPEN/ASPEN guidelines. The ESPEN guidelines recommend around 20–25 kcal/kg/day and 1.3 gm/kg/day of proteins. According to the ASPEN guidelines, the calories and proteins recommended are 25–30 kcal/kg/day and 1.2–2 gm/kg/day of proteins respectively.[6,7] The NUTRIREA3 study showed no difference in mortality in low vs standard calories and proteins.[8] Recent systematic review and meta-analysis evaluating the effect of permissive underfeeding vs standard feeding showed no difference in overall mortality.[9] Brazilian study on targets and prescription in the critically ill observed inadequacies in achieving nutrition targets, resulting in a negative nutritional balance.[10] A study done in the surgical ICU showed cumulative calorie and protein deficits were associated with prolonged ICU stay, fewer ventilator-free days, and increased complications.[11] There are limited Indian studies describing nutrition prescriptions.

We aimed to study the approximate weight-based nutritional prescription and its effect on ICU mortality in critically ill patients.

Materials and Methods

After institutional ethical committee approval, the study was conducted from 1st July 2018 to 31st March 2019. Informed consent was obtained from the legally acceptable representatives. The inclusion criteria were patients >18 years of age admitted to the ICU (medical and surgical). The patients who were readmitted and patients who were terminally ill were excluded. Strengthening the reporting of observational studies in epidemiology (STROBE)

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Table 1: Baseline characteristics and outcomes

Parameters	*All N = 100*	*Survivors N = 70*	*Non-survivors N = 30*	*p-value*
Age[¥]	48.63 (16.25)	47.02 (16.91)	52.44 (14.11)	0.132
Gender	M/F 62/38 (62/38)	M/F 44/26 (62.86/37.14)	M/F 18/12 (60/40)	0.787
Invasive mechanical ventilation	89 (89)	61 (87.14)	28 (93.33)	0.365
Comorbidities				
Diabetes	31 (31)	21 (30)	10 (33.33)	0.741
Cardiovascular	37 (37)	29 (41.43)	8 (26.67)	0.161
Respiratory	46 (46)	28 (40)	18 (60)	0.066
Abdomen	19 (19)	13 (18.57)	6 (20)	0.867
Renal	31 (31)	20 (28.57)	11 (36.67)	0.422
Autoimmune	17 (17)	9 (12.86)	8 (26.67)	0.092
APACHE II score	21.42 (6.51)	21.52 (6.89)	21.16 (5.65)	0.801
SOFA score	8.48 (3.47)	8.53 (3.41)	8.36 (3.67)	0.824
mNUTRIC score*	5 (3–6)	5 (3–6)	5 (3–6)	0.730
Time to initiation of RT feed (hrs)*	6 (3.75–13.5)	6 (4–14)	5.5 (3.5–13)	0.854
Admission diagnosis				
Sepsis	53 (53)	35 (50)	18 (60)	0.359
Surgical	5 (5)	4 (5.71)	1 (3.33)	0.617
Secondary outcomes				
Glucose variability coefficient of variation (CV)	38.96 (13.45)	36.99 (13.04)	43.83 (13.46)	0.031
ICU length of stay*	8 (6–12)	8 (6–10)	10.5 (6–15)	0.040
Duration of mechanical ventilation*	6 (4–10)	5 (4–8)	9 (6–11)	0.009
Presence of infection	76 (76)	49 (70)	27 (90)	0.032
Blood	23 (23)	15 (21.43)	8 (26.67)	0.568
BAL	55 (55)	31 (44.29)	24 (80)	0.001
Urine	20 (20)	12 (17.14)	8 (26.67)	0.275

Values are number (%), [¥]Mean (Standard deviation), *Median (Interquartile range)

guidelines were followed. The baseline characteristics, age, gender, and comorbidities were collected. Acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA) scores were calculated. The nutrition risk in the critically ill (NUTRIC) score identifies patients at risk of malnutrition.[12] The modified NUTRIC score (mNUTRIC) doesn't include interleukin 6 (IL-6). We calculated mNUTRIC score. The approximate weight-based calories and proteins prescribed were collected over 7 days. The calories and protein deficit was calculated as the difference between prescribed and received calories or proteins. The minimum and maximum glucose values from day 1 to day 7 were collected. We calculated the mean of maximum and minimum glucose values and standard deviation (SD). The glucose variability determined by the CV was calculated as the SD divided by mean blood glucose.

The primary outcome was the effect of approximate weight-based nutrition prescription (calories and proteins) on ICU mortality. The secondary outcomes were glucose variability, infection rates, length of ICU stay, and duration of mechanical ventilation.

Statistical Analysis

The statistical analysis was performed using STATA™ (Version 14, College station TX). The continuous variables were presented as mean (SD) and median [interquartile range (IQR)] as applicable. The univariate analysis was performed by independent *t*-test or Mann–Whitney *U*-test as applicable. A mixed linear regression model was used for analyzing parameters over 7 days. We did group-based trajectory analysis to identify different patterns of the glucose levels observed over 7 days and their effect on ICU mortality.

Results

Baseline Characteristics

Among 100 patients studied 62% were males and 38% were females. The mean age of the patients was 48.63 (16.25) years. The proportion of patients having comorbid illnesses, including diabetes mellitus was similar among non-survivors and survivors. The mean APACHE II and SOFA scores were 21.42 (6.51) and 8.48 (3.47) respectively. The primary outcome of ICU mortality was 30%.

The baseline characteristics between survivors and non-survivors were similar, including disease severity scores and mNUTRIC scores (Table 1). The mean calories prescribed on day 1 was 1836 (208) kcal/day.

The median calorie deficit was higher on day 1, with no significant difference between survivors and non-survivors. From the day 2 onwards, the median calorie deficit ranged from 200–300 kcal in survivors and 50–250 kcal in non-survivors, with no significant difference between the two groups (Table 2). A calorie goal of 80% was achieved by day 3. Similarly, proteins prescribed and received were comparable between survivors and non-survivors (Table 3).

The secondary outcomes were significantly different among survivors and non-survivors, with increased length of ICU stay and duration of mechanical ventilation in non-survivors (Table 1). The infection rates determined based on the positive culture report were significantly higher in non-survivors than survivors ($p = 0.032$). Among the various infections, bronchoalveolar lavage (BAL) culture positivity was higher in non-survivors than survivors ($p = 0.001$) (Table 1).

Table 2: Comparison of calorie deficit among survivors and non-survivors

Parameter	*N*	*Survivors*	*Non-survivors*	*p-value*
Day 1 calorie deficit	80	1125 (562–1545)	1150 (837–1550)	0.681
Day 2 calorie deficit	80	300 (50–637)	250 (–175–725)	0.249
Day 3 calorie deficit	72	225 (0–812)	50 (–75–375)	0.142
Day 4 calorie deficit	56	200 (0–600)	150 (0–475)	0.403
Day 5 calorie deficit	47	275 (150–677)	150 (0–750)	0.358
Day 6 calorie deficit	40	275 (50–675)	150 (0–425)	0.247
Day 7 calorie deficit	31	200 (0–750)	100 (–200–550)	0.471

Median (Interquartile range)

Table 3: Comparison of proteins prescribed and received by mortality

Parameter	*N*	*Proteins*	*Survivors*	*Non-survivors*
Day 1	66	Prescribed	92.4 ± 9.08	93.0 ± 7.32
	66	Actual received	43.1 ± 29.3	41.5 ± 26.7
Day 2	69	Prescribed	95.5 ± 9.4	88.5 ± 15.9
	66	Actual received	77.8 ± 21.8	79.1 ± 27.8
Day 3	66	Prescribed	96.3 ± 10.2	91.0 ± 7.2
	60	Actual received	79.9 ± 23.6	82.0 ± 25.7
Day 4	54	Prescribed	95.5 ± 8.6	93.7 ± 10.2
	52	Actual received	79.7 ± 21.7	79.5 ± 18.6
Day 5	54	Prescribed	97.0 ± 10.2	94.3 ± 10.9
	38	Actual received	78.5 ± 20.3	79.3 ± 29.1
Day 6	46	Prescribed	97.8 ± 11.3	96.2 ± 11.2
	35	Actual received	83.3 ± 14.7	84.2 ± 12.2
Day 7	27	Prescribed	97.6 ± 12.0	94.0 ± 9.7
	26	Actual received	88.7 ± 17.9	77.8 ± 25.9

Mean ± SD, *p*-value was >0.05 for proteins prescribed and actually received during 7 days

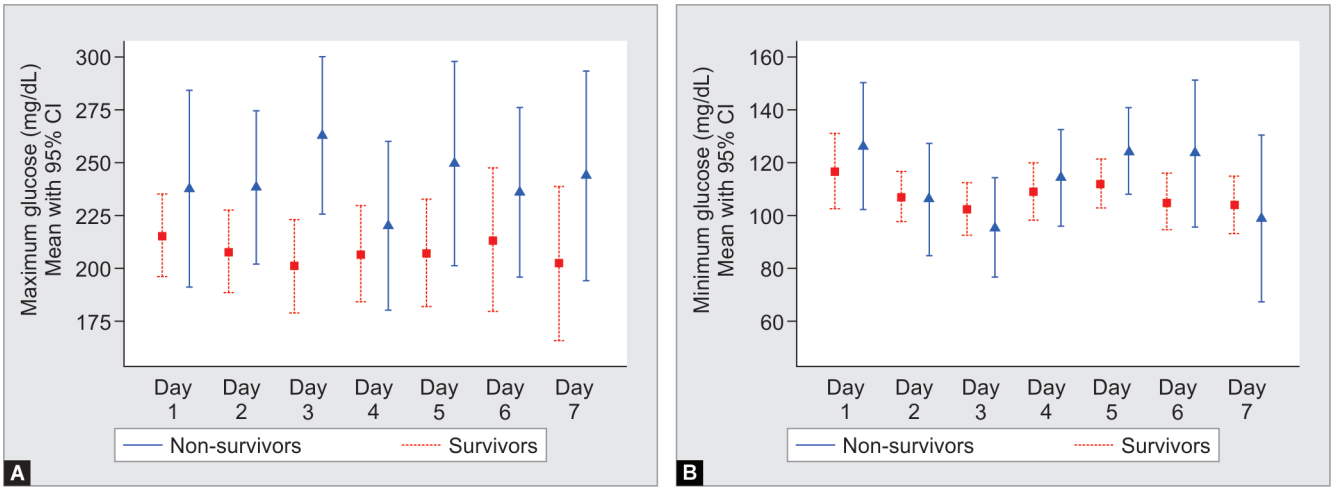
Glucose Variability

The maximum glucose values on day 1 were 236.9 (113.1) mg/dL and 214.4 (77.6) mg/dL among non-survivors and survivors respectively ($p = 0.289$). Similarly, minimum glucose values on day 1 were 129.6 (52.3) mg/dL and 121.3 (48.5) mg/dL among non-survivors and survivors respectively ($p = 0.489$). The maximum and minimum glucose values over 7 days were compared with the ICU mortality by mixed linear regression model (Fig. 1). A significant time effect ($p = 0.013$) and interaction effect ($p = 0.004$) were noted for maximum glucose levels indicating significantly higher variability in the maximum glucose level among non-survivors compared to survivors (Fig. 1A). However, for minimum glucose values, only a significant time effect was noted ($p = 0.047$) (Fig. 1B). In 100 patients 2 patients developed severe hypoglycemia defined as blood sugar <40 mg/dL. The mean blood glucose level among survivors and non-survivors was not statistically significant ($p = 0.057$). The CV was significantly higher in non-survivors than survivors (43.83 vs 36.99%, $p = 0.031$).

The group-based trajectory analysis was carried out to assess the pattern in the maximum glucose variability among ICU patients. Results revealed two latent classes over time based on the 7-day maximum glucose values. Latent class I (optimum glucose) consisted of 65% and latent class II (higher glucose group) formed by 35% of the patients (Fig. 2). The latent class I trajectory pattern was characterized by optimum glucose values over time. The association of the latent trajectory pattern observed with mortality showed that although non-significant, the latent class II trajectory group had a higher proportion of mortality (40%) compared to the latent class I trajectory group (23%) ($p = 0.153$).

Discussion

In our study, approximate weight-based nutritional prescription and calorie deficits were not associated with the mortality. The calories and proteins were prescribed as 25–30 kcal/kg and 1.2–1.5 gm/kg/day, respectively. The calorie deficit observed on day 1 in survivors and non-survivors was 1125 (562–1545) kcal and 1150



Figs 1A and B: (A) Comparison of maximum glucose levels between survivors and non-survivors over 7 days; (B) Comparison of minimum glucose levels between survivors and non-survivors over 7 days

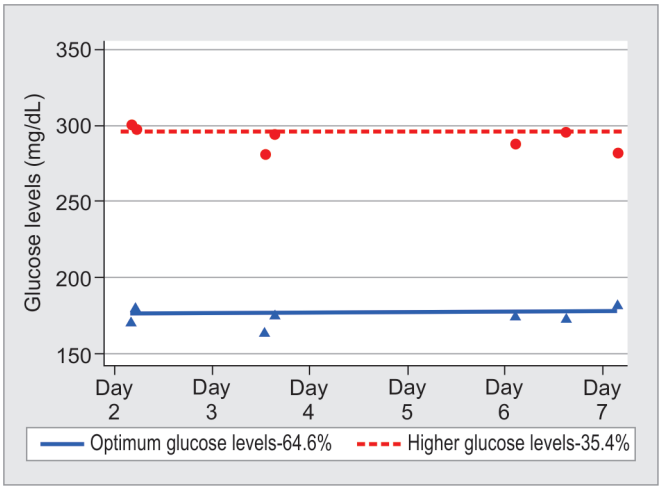


Fig. 2: Trajectory pattern observed in maximum glucose levels (mg/dL)

(837–1550) kcal respectively (Table 2). The mortality observed in this cohort was 30% (21–39%). This observation is similar to the studies comparing different nutritional calorie or protein administration on the mortality.[8,9]

The nutrition prescription in our study was 25–30 kcal/kg/day, similar to the observations from the Italian survey.[13] In the survey, the majority of the ICU calories were prescribed as 25 kcal/kg/day. Indirect calorimetry was used only in 8% of ICUs. Although indirect calorimetry is considered a gold standard, it is still not used in the majority of the ICUs, and calories prescription is largely based on Harris-Benedict's equation.

The approximate weight-based prescribed calories or proteins, and the deficits were not significant among the survivors and non-survivors. This was different from the findings observed in the study by Yeh, et al. in which cumulative calorie and protein deficits calculated for the first 14 days of ICU admission were associated with mortality in surgical patients.[11] A randomized controlled trial evaluating different protein prescriptions and their effect on mortality showed no difference in mortality and also cautioned regarding the harmful effects of higher protein targets in the specific groups based on the *post hoc* analysis.[14,15]

We did not find any difference in the severity of illness scores like APACHE II, SOFA, or in mNUTRIC scores among survivors and non-survivors. A recently published study in patients with high NUTRIC scores did not find any association between high NUTRIC scores and clinical outcomes.[16] In our study, we included a mixed ICU population (medical and surgical patients) and the median mNUTRIC score was 5 (3–6).

Among the secondary outcomes, variation in the maximum glucose levels over 7 days was found to be associated with mortality. Various indices are used for measuring glucose variability.[17–20] Coefficient of variation, maximum glucose difference, mean glucose difference, and J index to name a few. The study by Su et al. showed glucose variability defined based on the CV was an independent risk factor predicting mortality.[17] We also observed CV associated with the mortality [odds ratio 1.04 (1.003–1.077), $p = 0.036$].

Maximum glucose difference, glycemic gap, glycemic lability, and stress hyperglycemia ratio were the predictors of mortality, as shown in different studies.[21–24] The evidence for glucose control in the ICU has evolved from tight glucose control (81–108 mg/dL) to maintaining glucose levels below 180 mg/dL as an acceptable target.[25,26] In our study, although not significant trajectory analysis linear plot 1 had lower mortality (23%). This again emphasizes the importance of glucose time in range as a parameter for ICU patients as shown in the study by Ammar MA et al.[27]

We also observed that non-survivors had a higher risk of hospital-acquired infections. Among non-survivors, BAL culture positivity was higher in non-survivors. The higher risk of hospital-acquired infections in the non-survivors is possibly linked to hyperglycemia. There is limited information about pancreatic beta cell dysfunction leading to hyperglycemia in critically ill patients. This was proposed to be one of the mechanisms for the developing multiorgan failure in pediatric patients.[28] This needs to be studied in the critically ill adult population.

Strengths and Limitations

The strengths of our study include, we evaluated the effect of calorie and protein prescription in a longitudinal data over 7 days. The interesting observation was the glucose variability by CV and maximum glucose variability over 7 days were predictors of mortality. This indicates nutritional prescription can affect glucose variability.

The limitations of this study are that it was a single-center study. The assessment and prescription of the calories and proteins were predominantly based on the Harris-Benedict equation. The calculation based on the actual body weight was not possible. The prescription was largely based on the approximate estimation of the patient's weight by the treating team. In the majority of the Indian ICUs, beds with inbuilt weight measurement are not available. The estimated body mass index (BMI) in males and females based on the demispan was 22.82 (0.48) kg/m^2 and 20.93 (1.12) kg/m^2 respectively. In our ICU demispan is routinely measured to calculate predicted body weight. The predicted body weight derived from the demispan could have influenced the nutrition prescription. Enteral feeding was the preferred route in this cohort irrespective of the mixed ICU population involved. Hence, the comparison of enteral vs parenteral route could not be made.

Future studies are required to examine the effect of nutritional prescription on glucose variability. Also, the effect of critical illness causing pancreatic cell dysfunction needs to be investigated in adult critically ill patients. Measurement of lean body weight will be helpful in correctly administering calories and proteins.[29]

Conclusion

This study showed calorie or protein deficit was not associated with the mortality. The maximum glucose variability and CV were the predictors of ICU mortality. Future studies on nutrition should focus on the effect of nutrition on glycemic control and different indices of glucose variability.

Ethical Committee approval and CTRI registration: (IEC 94/2018, CTRI/2018/06/014625).

Authors Contributions

AAH: Concept, design, conduct, data analysis and writing and approving final draft; SS: Helped in statistical analysis. All authors have approved the final draft.

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