ORIGINAL ARTICLE

Combined Effect of the Timing of Initiation of Nutrition and Nutrition Risk on Outcomes in a Mixed Intensive Care Unit of a Tertiary Hospital in a Middle-income Country

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Abstract

Background: The importance of nutrition in the critically ill is well known but its practice is varied globally. Determining the nutrition risk is important to help improve outcomes.

Materials and methods: A prospective observational study involved patients admitted to the intensive care unit (ICU) who stayed for at least 48 hours. The demographics of participants modified the NUTRIC score, and comorbidities were assessed. The timing of nutrition initiation was noted to get two main cohorts: Early (within 48 hours of admission) and delayed (after 48 hours of admission). All the patients were followed for a maximum of 30 days in the hospital to determine outcome variables such as mortality and length of hospital stay. The ICU-free days (30 minus days in ICU) and 30-day hospital-free days were calculated and recorded for each patient.

Results: A total of 489 patients, 59.9% were males, 75.5% were mechanically ventilated and total parenteral nutrition utilization was 13.2%. The prevalence of nutrition risk was 21.1%. The patients who had early nutrition constituted 36.6%. There was no difference in the primary outcome of ICU-free days between the two groups; 24 (19–25.5) and 24 (16–25) days, respectively; $p = 0.591$. The high modified NUTRIC score cohort had lower ICU-free days ($p < 0.001$), 30-day hospital-free days, and higher mortality; 18 (0–24) vs 25 days (20–26), $p < 0.001$.

Conclusion: The timing of the initiation of nutrition does not affect ICU-free days and 30-day hospital-free days irrespective of the nutrition risk on admission. A high modified NUTRIC score is associated with reduced ICU-free days and 30-day hospital-free days and increased mortality.

Keywords: 30-day hospital-free days, Early nutrition, ICU-free days, mNUTRIC score, Nutrition risk.

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Highlights

In a mixed intensive care unit (ICU), the timing of the initiation of nutrition does not affect mortality or the length of ICU stay regardless of the nutrition risk at the time of admission.

Introduction

The provision of nutrition to the critically ill has a central role to play in patient management and eventual outcomes. It is known that the provision of the nutritional needs of the critically ill patient must follow the early resuscitation of the patient. However, exactly how early to provide nutrition is not precisely known and whether this early provision of nutrition translates to measurable outcomes is controversial.[1–3]

A lot of patients admitted to the ICU have some nutritional deficits.[4] It is also probable that the severity of illness and nutritional status have a profound impact on the eventual outcomes of patients. The use of nutritional assessment tools allows the identification of at-risk patients and track their progress.[5] The modified NUTRIC score which is a validated tool, takes into account both of these factors and may be best suited to stratify the nutritional risk of patients. The tool has been found to predict mortality and it has been used in several studies that looked at the nutritional risk of patients in the ICU.[6–11]

Data related to the aforementioned issues from middle-income countries is insufficient to lead to adequate conclusions

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and there is likely to be demographic and practice variation from the West owing to socioeconomic variances and resource constraints.[12]

Even though there is unanimity on the importance and role of nutrition in the critically ill, there is still variation in practice and recommendations across the world.[13,14] The majority of the current data on nutritional practice is from Western countries with very limited data from the critical care units in the developing and middle-income countries such as India. The available data are either retrospective, small, or heterogeneous cohorts of patients.[15,16]

The combined effect of the time of initiation of nutrition in the ICU and the nutrition risk at admission on outcomes has not been widely studied.

The main objectives of this study were to determine the prevalence of nutritional risk and describe the feeding patterns (early and late nutrition) in the ICU. Their effect on patient outcomes (ICU-free days, 30-day hospital-free days, and mortality) was assessed.

Objectives

The main objective of this study was to determine the effect of the timing of initiation of nutrition and a high modified NUTRIC score on patient outcomes (ICU-free days, 30-day hospital-free days, and mortality).

The specific objectives were as follows:

- To determine the prevalence of nutritional risk in the mixed Intensive Care Units using the modified NUTRIC score.
- To determine the effect of nutritional risk on ICU-free days, 30-day hospital-free days, and mortality.
- To determine the effect of the timing of the initiation of nutrition (early or late nutrition) on ICU-free days, 30-day hospital-free days, and mortality.
- To determine the effect of the timing of the initiation of nutrition (early or late nutrition) on ICU-free days, 30-day hospital-free days, and mortality among the patients with a high modified NUTRIC score.

Materials and Methods

Ethical Clearance

The study was approved in 2019 by the Institutional Review Board of the Christian Medical College, Vellore India. The approval Reference Number is IRB:11727.

Study Design and Data Collection

This was a prospective observational study involving patients who stayed for at least 48 hours in three different ICUs in a Tertiary Hospital in India. The combined bed capacity of the three ICUs was 28 (13, 9, and 6). The monthly statistics show that 80–85% of the admitted patients are from the surgical disciplines and 15–20% are medical with 70–75% invasive ventilatory requirements.

The study included all patients, 16 years and above, admitted to the ICUs who stayed for at least 48 hours and gave informed consent.

Excluded patients included pregnant women, those diagnosed with hematological malignancies, those undergoing hepatic surgery, those with a prior diagnosis of liver disease, and those who were already on total parenteral nutrition (TPN).

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Conflict of interest: None

Procedure Used

The data collection for the study occurred between January and June 2019 after obtaining approval and ethical clearance from the Institutional Review Board (IRB Number: 11727; dated 19 Dec 2018).

The ICU patients on admission were reviewed daily to identify the patients who met the inclusion criteria. Once identified, the patients with compos mentis were approached directly while others, their relatives, or next of kin were approached to obtain a signed informed consent. Once recruited, the patients had their demographics taken and the timing of initiation of nutrition was noted to get two main cohorts: Early cohort (within 48 hours of admission), and delayed cohort (after 48 hours of admission).

Their baseline electrolytes (sodium, potassium, chloride, phosphate, calcium, and magnesium), arterial blood gas, APACHE II score, SOFA score, modified NUTRIC score and insulin requirement were noted at the time of starting nutrition. Comorbidities like diabetes and polytrauma were documented. The patients with a modified NUTRIC score of less than five were classified as a low-risk cohort while those with a score of 5 or more were classified as a high-risk cohort. All the recruited patients were followed for a maximum of 30 days in the hospital, starting from the day of ICU admission to determine outcome variables such as mortality, length of hospital stay, and re-admission to the ICU.

The ICU-free days (30 minus days in ICU) and 30-day hospital-free days were calculated and recorded for each patient.

Nutritional Support

In this study, patients were deemed to be receiving nutrition when they were feeding orally, had tube feeding, or were receiving TPN. Additionally, if patients received supplementation with glucose, amino acids, and fat emulsions, they were considered to have received nutrition.

Outcomes

The primary outcome was ICU-free days [Calculated as 30 – days spent in the ICU over a period of 30 days]. For patients who died in the ICU, the ICU-free days were zero (0)].

The secondary outcome was 30-day hospital-free days [Calculated as 30 – days spent in the hospital over 30 days]. For patients who died during admission, hospital-free days were zero (0)].

Sample Size

The primary objective of the study was to determine the effect of the timing of initiation of nutrition (early vs delayed) on ICU-free days. For the sample size calculation, the statistical input was taken from the pilot study results which were conducted in the ICU between 1 Sept 2018 and 31 Oct 2018. Considering the average difference of 2.5 days (more than 48 hours) on the ICU-free days between the early nutrition group and delayed nutrition group, 80% power, 5% significance level, and two-sided test, the sample size was estimated as 352 patients. Within the data collection period, we were able to collect data of 489 patients which is more than the sample size.

Statistical Analysis

For continuous data, the descriptive statistics *n*, mean, SD, and for nonnormally distributed interval data and ordinal data, median (interquartile range [IQR]) was presented. Number of patients and percentage were presented for categorical data. The non-parametric Mann-Whitney U-test was applied to the data. The Pearson Chi-Squared test was used to find the association between categorical variables.

To assess the factors associated with mortality, logistic regression was performed. The point estimate was reported as an odds ratio (95% confidence interval). To assess the association of factors with ICU-free days, the zero-inflated negative binomial model was performed.

All tests were two-sided at $\alpha = 0.05$ level of significance. All data analyses were performed with Stata version 13 (Stata Corp, College Station, TX, USA).

Results

There were 489 patients in the study, 293 (59.9%) were males and 75.5% received mechanical ventilation. Utilization was 13.2%, enteral nutrition accounted for 58.7%, and 28.1% received calories mainly through dextrose infusions. The baseline characteristics of the patients are shown in Table 1.

The nutrition risk among the patients using the modified NUTRIC score was 21.1%. As per Tables 2 and 3 a high nutrition risk on admission correlates with lower ICU-free days and 30-day hospital-free days, $p < 0.001$ in both instances. A similar relationship exists for mortality, $p < 0.001$ with an odds ratio of 4.92 (Tables 4 and 5).

On the timing of initiation of nutrition, Early nutrition (Initiated feeding within 48 hours of admission) constituted 21.1%, and delayed nutrition (initiated feeding after 48 hours of admission) constituted 78.9%. As shown in Table 2, there was no difference

Table 1: General characteristics of the patients recruited into the study ($n = 489$)

Characteristics	*All patients (n = 489) Median (IQR) Number (%)*	*Low nutrition risk (mNUTRIC score ≤ 4, n = 386) Median (IQR) Number (%)*	*High nutrition risk (mNUTRIC score ≥ 5, n = 103) Median (IQR)Number (%)*	*p-value*	*Early nutrition (within 48 hrs)*	*Delayed nutrition (after 48 hrs)*	*p-value*
Age (years)	48.0 (33.0, 60.0)	45.0 (30.0, 57.0)	60.0 (48.0, 69.0)	<0.001	46.0 (31.75, 58.0)	51.0 (35.0, 63.0)	0.010
Sex							
Female	196 (40.1)	167 (43.3)	29 (28.2)	0.00	136 (43.9)	60 (33.5)	0.024
Male	293 (59.9)	219 (56.7)	74 (71.8)	5	174 (56.1)	119 (66.5)	
BMI (kg/m^2)	24.22 (21.48, 27.68)	24.22 (21.32, 27.35)	25.14 (22.03, 29.05)	0.283	24.22 (21.02, 27.68)	24.69 (22.03, 27.55)	0.345
Vasoactive therapy							
No	289 (59.1)	245 (63.5)	44 (42.7)	<0.001	182 (58.7)	107 (59.8)	0.849
Yes	200 (40.9)	141 (36.5)	59 (57.3)		128 (41.3)	72 (40.2)	
Mechanical ventilation							
Yes	396 (75.5)	278 (72.0)	91 (88.3)	0.001	226 (72.9)	143 (79.9)	0.084
No	120 (24.5)	108 (28.0)	12 (11.7)		84 (27.1)	36 (20.1)	
APACHE II	15.0 (10.0, 20.0)	12.50 (9.0, 17.0)	24.0 (21.0, 28.0)	<0.001	14.0 (10.0, 19.0)	16.0 (11.0, 22.0)	0.031
SOFA	5.0 (3.0, 8.0)	4.50 (2.0, 7.0)	10.0 (7.0, 12.0)	<0.001	5.0 (3.0, 8.0)	6.0 (3.0, 9.0)	0.086
mNUTRIC score	3.0 (2.0, 4.0)	2.0 (1.0, 3.0)	6.0 (5.0, 6.0)	<0.001	3.0 (2.0, 4.0)	3.0 (1.0, 5.0)	0.498
Diabetes							
Absent	318 (65.0)	271 (70.2)	47 (45.6)	<0.001	214 (69.0)	104 (58.1)	0.015
Present	171 (35.0)	115 (29.8)	56 (54.4)		96 (31.0)	75 (41.9)	
Trauma							
No	451 (92.2)	351 (90.9)	100 (97.1)	0.038	287 (92.6)	164 (91.6)	0.702
Yes	38 (7.8)	35 (9.1)	3 (2.9)		23 (7.4)	15 (8.4)	
Outcome							
ICU-free days	24.0 (16.0, 25.0)	25.0 (20.0, 26.0)	18.0 (0.0, 24.0)	<0.001	24.0 (16.0, 25.25)	24.0 (16.0, 25.0)	0.539
Hospital-free days	18.0 (4.0, 22.50)	18.50 (9.0, 23.0)	7.0 (0.0, 21.0)	<0.001	18.0 (5.0, 22.0)	18.0 (0.0, 23.0)	0.957
In-hospital mortality							
No	410 (83.8)	345 (89.4)	65 (63.1)	<0.001	266 (85.8)	144 (80.4)	0.121
Yes	79 (16.2)	41 (10.6)	38 (36.9)		44 (14.2)	35 (19.6)	
ICU length of stay	4.0 (2.0, 7.0)	3.0 (2.0, 6.0)	5.0 (3.0, 10.0)	<0.001	3.0 (2.0, 8.0)	4.0 (2.0, 6.0)	0.600
Hospital length of stay	10.0 (6.0, 16.0)	10.0 (6.0, 16.0)	10.0 (5.0, 18.0)	0.356	11.0 (6.0, 16.0)	9.0 (6.0, 16.0)	0.132

Table 2: Outcomes of ICU patients according to the nutrition risk and time of initiating nutrition

	Nutrition risk			*Initiation of nutrition*		
Clinical outcome	*Low nutrition risk (mNUTRIC score ≤ 4, n =386) Median (IQR) Number (%)*	*High nutrition risk (mNUTRIC score ≥ 5, n =103) Median (IQR) Number (%)*	*p-value*	*Early nutrition (within 48 hrs)*	*Delayed nutrition (after 48 hrs)*	*p-value*
Outcome						
ICU-free days	25.0 (20.0, 26.0)	18.0 (0.0, 24.0)	<0.001	24.0 (16.0, 25.25)	24.0 (16.0, 25.0)	0.539
Hospital-free days	18.50 (9.0, 23.0)	7.0 (0.0, 21.0)	<0.001	18.0 (5.0, 22.0)	18.0 (0.0, 23.0)	0.957
In-hospital mortality						
No	345 (89.4)	65 (63.1)	<0.001	266 (85.8)	144 (80.4)	0.121
Yes	41 (10.6)	38 (36.9)		44 (14.2)	35 (19.6)	
ICU length of stay	3.0 (2.0, 6.0)	5.0 (3.0, 10.0)	<0.001	3.0 (2.0, 8.0)	4.0 (2.0, 6.0)	0.600
Hospital length of stay	10.0 (6.0, 16.0)	10.0 (5.0, 18.0)	0.356	11.0 (6.0, 16.0)	9.0 (6.0, 16.0)	0.132

Table 3: The combined effect of the timing of initiation of nutrition and nutrition risk on ICU-free days, 30-day-hospital-free days, and mortality

	Early nutrition	*Delayed nutrition*	
Patient cohort and outcome (High nutrition risk)	*Median (IQR)*	*Median (IQR)*	*p-value*
Patients with a high modified NUTRIC score (nutrition risk) *n* = 103			
ICU-free days	17 (0, 24)	18 (0, 23)	0.908
30-day-hospital-free days	2.5 (0, 21)	11 (0, 20.5)	0.776
Mortality, *n* (%)	18 (36.0%)	20 (37.7%)	0.855
	Early nutrition	*Delayed nutrition*	
Patient cohort and outcome (Low nutrition risk)	*Mean (SD)*	*Mean (SD)*	*p-value*
Patients with a high modified NUTRIC score (nutrition risk) *n* = 386			
ICU-free days	20.3 (8.5)	20.8 (8.4)	0.606
30-day-hospital-free days	15.5 (8.7)	15.8 (9.4)	0.762
Mortality, *n* (%)	26 (10.0%)	15 (11.9%)	0.569

Table 4: Factors associated with mortality using logistic regression

Factor	*Odds ratio (95% CI)*	*p-value*	*Adjusted odds ratio (95% CI)*	*p-value*
Age (years)	1.02 (0.99, 1.03)	0.092		
Modified nutric score	1.61 (1.39, 1.85)	<0.001		
Body mass index (kg/m^2)	0.99 (0.95, 1.04)	0.863		
APACHE II score	1.12 (1.08, 1.15)	<0.001		
SOFA (baseline)	1.22 (1.14, 1.30)	<0.001		
Nutrition risk (high)	4.92 (2.94, 8.23)	<0.001	3.67 (2.13, 6.31)	<0.001
Initiation of nutrition (after 48 hrs)	1.47 (0.90, 2.39)	0.122		
Parenteral type binary (TPN)	1.16 (0.54, 2.48)	0.709		
Insulin required	2.85 (1.55, 5.24)	0.001	1.71 (0.88, 3.32)	0.115
Ventilated	3.91 (1.75, 8.76)	0.001	2.64 (1.15, 6.09)	0.023
Shock	2.47 (1.51, 4.03)	<0.001	1.85 (1.10, 3.12)	0.021
DM (present)	1.25 (0.76, 2.04)	0.385		
Surgery done	0.56 (0.33, 0.93)	0.024		
Polytrauma	0.97 (0.39, 2.41)	0.949		

95% CI, 95% confidence interval

in the ICU-free days and 30-day hospital-free days between early nutrition and delayed nutrition; $p = 0.591$ and $p = 0.659$, respectively. Table 3 also shows that in patients with a high modified NUTRIC score, the timing of the initiation of nutrition did not affect outcomes. Multivariate logistic regression revealed that APACHE-II, baseline SOFA, insulin requirement, mechanical ventilation, and a high mNUTRIC score were independent predictors of mortality.

Table 5: Zero-inflated negative binomial (ZINB) regression coefficients for the number of ICU-free days

	Logit part		*Negative binomial part*	
Clinical factor	*OR (95% CI)*	*p-value*	*IRR (95% CI)*	*p-value*
Nutrition risk (high)	3.53 (2.08, 6.05)	0.0001	0.92 (0.87, 0.98)	0.010
Insulin required (yes)	1.90 (0.99, 3.63)	0.051	1.02 (0.95, 1.09)	0.596
Ventilated (yes)	2.48 (1.13,5.47)	0.024	0.94 (0.90, 0.98)	0.005
Shock	1.84 (1.09, 3.03)	0.020	0.99 (0.95, 1.05)	0.729

IRR, incident risk ratio; OR, odds ratio; 95% CI, 95% confidence interval

Discussion

In this study, the prevalence of patients with high nutrition risk on admission was found to be 21.1%. This result agrees with that of Wang et al.[17] who reported 28.1% in China. Two Indian ICU studies, one by Renuka et al.[18] reported a nutritional risk of 42.5% using the modified NUTRIC score and another study by Chakravarty et al.[19] documented a risk of 39.6% using the subjective global nutritional assessment. The difference in the prevalence of high nutritional risk may be due to the patient cohorts that were studied- the first study had a cohort of patients that were exclusively mechanically ventilated and in the second study 10% of patients had cancer. The assessment tool used was also different in the study by Chakravarty et al.[19] Renuka et al.[18] demonstrated a predictive effect of a high nutrition risk on mortality.

In our study, we found that early nutrition (whether the patients had a high or low modified NUTRIC score) did not impact ICU-free stay which was our primary outcome of interest. We also found no significant effect on 30-day hospital-free days or mortality. This finding is similar to a study by Ojo et al.[20] and other studies where the outcome was not altered by early feeding. There could be various reasons for this. Perhaps despite following standard protocols regarding feeding, the patient population was too sick to benefit from early feeding (high nutritional risk, high APACHE score, high SOFA score). Probably other factors like quality of resuscitation have more impact on outcomes than early feeding.

A recent Cochrane review of seven randomized control trials and 345 participants concluded that there was insufficient evidence to conclude that early feeding had an impact on outcomes compared to delayed feeding.[21] Murthy et al.[15] found that it had no effect on ICU length of stay but reduced hospital length of stay in an observational study from Karnataka, south India.

In this study, we found that a high nutrition risk is associated with higher mortality, fewer ICU-free days, and fewer 30-day hospital-free days. This association between a high modified NUTRIC score and higher mortality, fewer 30-day hospital-free days, and fewer ICU-free days may be explained by the relationship between mNUTRIC and the patient's level of disease acuity. Generally, considering the parameters that are assessed in mNUTRIC, score (such as APACHE II score and SOFA score), a higher mNUTRIC score may be indicative of a higher disease acuity which impacts negatively on mortality. More nutrition-specific indicators of high-risk nutrition could be the SGA score.

The study also depicts that the utilization of TPN is relatively low, accounting for 13.2% of the patients. Enteral nutrition accounted for 58.7%, with the rest of the patients receiving calories mainly through dextrose infusions. There is generally a low utilization of TPN in lower- and middle-income countries mainly due to cost. However, this finding aligns with the recommendations of ASPEN and ESPEN that enteral feeding should be the preferred route for nutritional support. The low utilization of TPN and a relatively higher use of dextrose-based parenteral nutrition were reported by Daphnee and Bharadwaj.[22–24]

There are some limitations to our current study. First, even though it is a mixed ICU study, the majority of the patients were surgical (excluding neurosurgical and cardiac patients because there were separate ICUs for them), and given the heterogeneous nature of critical illness, the findings may not be applicable in all cohorts of critically ill patients. It may better suit ICUs with predominantly surgical patients. Secondly, there was no threshold of a minimally accepted amount of calories that was deemed adequate. Additionally, the heterogeneous nature of the patients occasioned by the inclusion of different age groups, pathologies, and comorbidities of the patients makes it difficult for the results to be extrapolated to all ICU patient cohorts.

Conclusion

The nutritional risk in the mixed Intensive Care Units using the modified NUTRIC score is 21.10%. There is a significant reduction in ICU-free days and 30-day hospital-free days as well as an increase in mortality in patients with a high nutrition risk. Early or late nutrition does not affect ICU-free days, 30-day hospital-free days, and mortality, irrespective of the nutrition risk.

Clinical Significance

This study is significant because it highlights the effect of the timeliness (early or late) of nutritional intervention on both high and low nutrition risk. A lot of studies have looked at either the effect of timeliness of nutrition or nutrition risk on clinical outcomes but not the combined effect of timeliness of nutrition and nutrition risk. The study was conducted in a middle-income country where data is relatively rare compared to the developed countries.

Authors Contribution

Moses Siaw-Frimpong: Conceptualization, methodology, original draft, data curation, review, and editing. Pritish J. Korula: Conceptualization, methodology, original draft, data curation, review, and editing. Reka Karuppusami: Data curation, formal analysis, review, and editing. Kandasamy Subramani: Conceptualization, supervision, review, and editing. Nana Fosua Gyapon: Writing, review, and editing. Rajendran Udhay Chander: Conceptualization, supervision, review, and editing. Shoma Rao: Conceptualization, supervision, review, and editing. William Addison: Conceptualization, review, and editing.

Declaration

We declare that this work is original and conducted by the listed Authors. The manuscript has neither been published nor presented to another journal for publication.

Ethical Clearance

The study was approved in 2019 by the Institutional review Board of the Christian Medical College, Vellore India. The approval reference number is **IRB:11727**.

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