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Early goal enteral nutrition associated with decreased in-hospital death in mechanically ventilated critically ill adults: a retrospective cohort study

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ABSTRACT

Introduction Early enteral nutrition (EN) in critically ill adult patients is thought to improve mortality and morbidity; expert guidelines recommend early initiation of EN in critically ill adults. However, the ideal schedule and dose of EN remain understudied.

Study objective Our objective was to evaluate the relationship between achieving 70% of recommended EN within 2 days of intubation ('early goal EN') and clinical outcomes in mechanically ventilated medically critically ill adults. We hypothesised that early goal EN would be associated with reduced in-hospital death.

Methods We conducted a retrospective cohort study of mechanically ventilated adult patients admitted to our medical intensive care unit during 2013–2019. We assessed the proportion of recommended total EN provided to the patient each day following intubation until extubation, death or 7 days whichever was shortest. Patients who received 70% or more of their recommended total daily EN within 2 days of intubation (ie, 'baseline period') were considered to have achieved 'early goal EN'; these patients were compared with patients who did not ('low EN'). The primary outcome was in-hospital death; secondary outcomes were successful extubation and discharge alive.

Results 938 patients met eligibility criteria and survived the baseline period. During the 7-day postintubation period, 64% of all patients reached 70% of recommended daily calories; 33% of patients achieved early goal EN. In unadjusted and adjusted models, early goal EN versus low EN was associated with a lower incidence of in-hospital death (subdistribution HR (SHR) unadjusted=0.63, p=0.0003, SHR adjusted=0.73, p=0.02). Early goal EN was also associated with a higher incidence of successful extubation (SHR unadjusted=1.41, p<0.00001, SHR adjusted=1.27, p=0.002) and discharge alive (SHR unadjusted=1.54, p<0.00001, SHR adjusted=1.24, p=0.02).

Conclusions Early goal EN was associated with significant improvement in clinical metrics of decreased in-hospital death, increased extubation and increased hospital discharge alive.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Though early initiation of enteral nutrition (EN) in critically ill patients has been established as an important step to recovery, optimal feeding parameters, including the number of calories that should be provided, remain unknown and an important target to improve critical illness outcomes.

WHAT THIS STUDY ADDS

⇒ Our objective was to evaluate the relationship between achieving 70% of recommended EN within 2 days of intubation ('early goal EN') and clinical outcomes in critically ill adults. Via a retrospective cohort study of mechanically ventilated adult patients admitted to the medical intensive care unit, we found that achieving early goal EN was associated with significantly reduced in-hospital death, increased successful extubation and increased discharge alive.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early goal EN was associated with significant improvement in clinical outcomes; further prospective studies should investigate the lower and upper limits of the early EN dose needed to benefit critically ill patients.

INTRODUCTION

Early initiation of enteral nutrition (EN) in critically ill patients has been established as an important step to recovery.[1–3] Studies have shown the delivery of EN therapy allows for physiological changes in the gastrointestinal tract, preventing an increase in intestinal permeability and systemic infection.[1 4 5] However, the specifics of EN delivery, such as the method of administration (continuous vs intermittent timing), rate of enteral feeds (full feeds vs trophic feeds) and dose of enteral feeds (proportion of recommended daily calories delivered), have not been rigorously studied. In fact, continuous feeds tend to be the default of care in most medical intensive care units (MICU) despite the lack of evidence to guide this practice.[6] Furthermore, because critically ill patients require

numerous interventions, feeds are frequently interrupted and many patients fail to receive the recommended EN caloric intake.[7 8] Optimal feeding parameters that can be pragmatically achieved remain unknown and an important target to improve critical illness outcomes.[2 3]

Optimal dose of enteral feeds has been particularly challenging to determine. The current guidelines from the American Society for Parenteral and Enteral Nutrition and Society of Critical Care Medicine recommend efforts be made to provide greater than 80% of estimated goal calories within 48–72 hours of ICU admission in patients who are severely malnourished or at high nutrition risk.[1] However, these recommendations are based on expert consensus, as published literature on the need for full EN is not only sparse but also inconsistent. For example, one prospective cohort study in adult ICUs showed reaching 33%–65% of target feeds improved outcomes versus reaching less or more of target feeds; outcomes included rates of hospital discharge alive and spontaneous ventilation.[9] In contrast, a randomised controlled trial of permissive underfeeding (40%–60% of goal) versus standard feeding group (70%–100% of calculated caloric requirements) in nearly 900 mixed ICU patients showed no difference in 90-day mortality, ICU and hospital length of stay or adverse events.[10] Finally, the EDEN trial of 1000 adult patients with acute lung injury compared initial trophic feeding (400 kcal per day) with full feeding goals (an average receipt of 1300 kcal per day) and demonstrated no difference in outcomes.[11]

In fact, several studies have suggested harm in both underfeeding and overfeeding during critical illness. While specific caloric contributions are variable, it is well established that endogenous energy production is preserved in the early days of critical illness.[12] Therefore, full exogenous enteral feeding may lead to overfeeding in some cases. Although precise measurement of energy needs via indirect calorimetry is considered the gold standard and endorsed in guidelines,[1] such measures are not routinely performed in most centres. A comparison of requirements estimated via predictive equations versus indirect calorimetry suggests that both underdosing and overdosing may occur. In view of this, Zusman *et al* evaluated the association of administered calories (as a percentage of resting energy expenditure obtained by indirect calorimetry) and 60-day mortality.[13] The study suggested a U-shaped mortality curve, such that caloric intake of 70% of measured resting energy expenditure conferred a survival benefit while the higher and lower intake was associated with harm. Similarly, in the large prospective cohort study examining approximately 7900 patients across 352 ICUs, patients who received more than two-thirds of their prescribed calories had lower mortality compared with those with those receiving less than one-third; as a continuous variable, increasing calories received correlated with improved mortality.[14]

Our objective was to assess the benefit of achieving sufficient feeds early in critical illness with a pragmatic threshold of 70% given the equipoise in prior data showing lack of harm and possible benefit for reaching 60%–80% of recommended calories in a set of highly heterogeneous studies.[9–14] We tested associations between achieving greater than 70% of the total recommended EN caloric intake within 2 calendar days of intubation ('early goal EN') and clinical outcomes in a population of medically critically ill mechanically ventilated patients admitted to the MICU. We hypothesised that early goal EN would be associated with decreased in-hospital death (primary outcome) and increased successful extubation and/or discharge alive from the hospital (secondary outcomes) when compared with our control group who did not achieve early goal EN ('low EN').

MATERIALS AND METHODS

Study design

This was a retrospective cohort study.

Patient and public involvement

There was no patient or public involvement in the design of this study.

Setting

We identified critically ill adult patients who were admitted to our hospital's two MICUs from 2013 to 2019. These two MICUs are located on separate campuses of a single tertiary academic hospital but serve the same patient population and operate with the same protocols and a common provider pool (ie, staff work at both campuses).

Participants

Our study sample included all patients aged 18–99 years who were intubated within 24 hours of admission to our MICU and did not have a tracheostomy or enterostomy tube at the time of MICU admission, did not initiate EN or parenteral nutrition prior to MICU admission, had not been transferred from an ICU of differing subspecialty (such as the neurological or surgical ICU) during their hospital stay, was not breastfeeding or pregnant and was not admitted post cardiac arrest with subsequential devastating neurological impairment leading to withdrawal of care. We then excluded patients with missing nutrition data, and patients who died or who were extubated during the baseline period.

Data collection

The initial dataset was automatically extracted from the EPIC electronic medical record. This automated chart review was followed by a manual review to further assess eligibility criteria and obtain nutritional parameters. Continuous feeding around the clock is the standard feeding schedule used in our MICU; caloric needs were estimated using predictive equations per unit protocols.

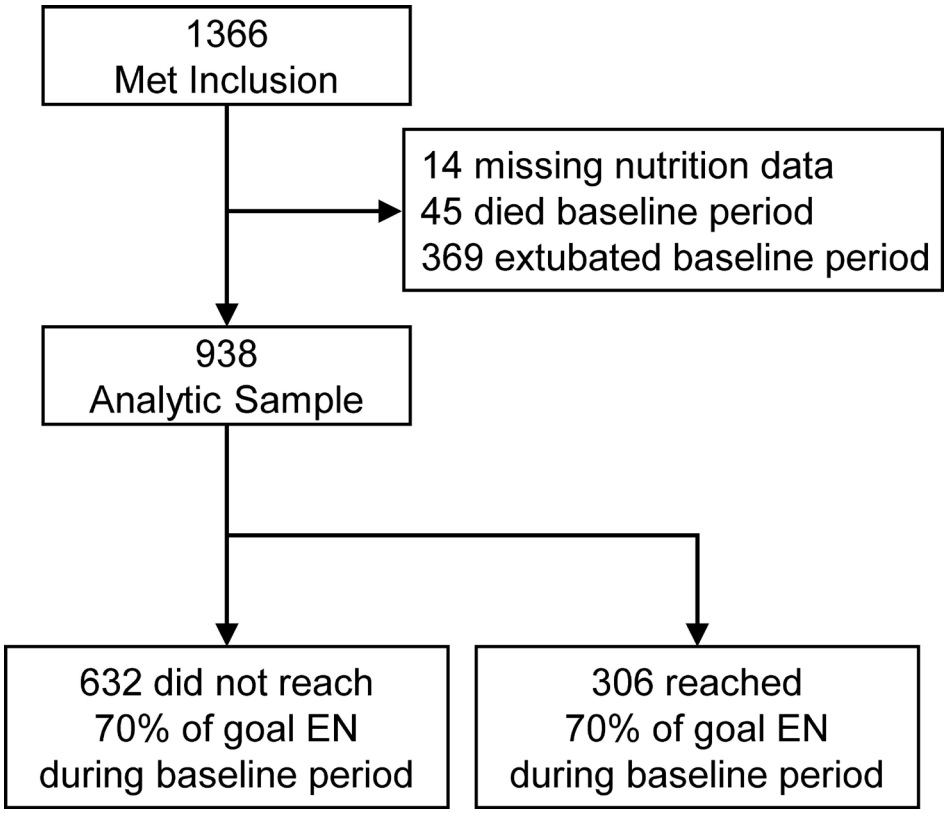

Figure 1 Study CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trial; EN, enteral nutrition.

Variables

We collected demographic and clinical data including age, sex, race, medical history, body mass index (BMI) and acute illness clinical course including, admission and discharge timing, intubation and extubation timing, medication use during MICU admission, and vital signs and laboratory data to support the calculation of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

For each patient, day of intubation was defined as study day 0, and nutrition data were extracted for the first 7 days following intubation (ie, until study day 7), successful extubation or death whichever was shortest. Successful extubation was defined as extubation without reintubation or death in 48 hours.[15] We collected nutritional data including recommended nutritional intake, daily volume of enteral feeds and formula used. Nutritional data were expressed as a percentage based on

Table 1 Baseline characteristics for all patients in the analytical sample divided by exposure (N=938)

Characteristic	Low EN* n=632	Early goal EN* n=306	P value
Age, mean±SD	62.9±16.1	65.2±16.3	0.04
Male sex, N (%)	357 (56.5)	139 (45.4)	<0.01
BMI, mean±SD	29.7±8.9	30.4±9.9	0.30
APACHE II, mean±SD	26.0±7.8	23.4±7.0	<0.01
Infection at baseline, N (%)	565 (89.4)	270 (88.2)	0.59
Vasopressors days 0–2, N (%)†	417 (66.2)	142 (46.7)	<0.01
Neuromuscular blockade, days 0–2, N (%)†	251 (39.8)	133 (43.8)	0.26
Died in hospital, N (%)	243 (38.4)	79 (25.8)	<0.01
Pre-existing hypertension, N (%)	420 (66.5)	219 (71.6)	0.24
Pre-existing diabetes, N (%)	247 (39.1)	126 (41.2)	0.71

*'Low EN' indicates patients who did not achieve 70% of recommended EN within 2 calendar days of intubation; 'Early goal EN' indicates patients who did achieve 70% of recommended EN within 2 calendar days of intubation.
†Control n=630; intervention n=304 for vasopressors and neuromuscular blockade during baseline period.
APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; EN, enteral nutrition.

Table 2 Proportion of recommended calories received during the baseline period

Nutrition variable	Low EN* n=632	Early goal EN* n=306	P value
Mean proportion of recommended calories received on day 1†: mean±SD	0.08±0.15	0.50±0.32	<0.001
Median proportion of recommended calories received on day 1: median (IQR)	0 (0.00–0.12)	0.44 (0.24–0.74)	<0.01
Mean proportion of recommended calories received on day 2†: mean±SD	0.22±0.21	0.94±0.31	<0.001
Median proportion of recommended calories received on day 2: median (IQR)	0.18 (0.00–0.38)	0.85 (0.83–1.04)	<0.01

*'Low EN' indicates patients who did not achieve 70% of recommended EN within 2 calendar days of intubation; 'Early goal EN' indicates patients who did achieve 70% of recommended EN within 2 calendar days of intubation.
†Day 1 indicates the first full calendar day following intubation. Day 2 indicates the second full calendar day following intubation; days 1 and 2 are part of the designated baseline period.
EN, enteral nutrition.

daily caloric intake (exclusive of propofol and protein supplements) divided by calories prescribed per nutritionist assessment. We defined the baseline period as study days 0, 1 and 2. Patients were classified as being in the intervention group (eg, achieving 'early goal EN') if they achieved at least 70% of recommended daily calories during this baseline period.

The primary study outcome was in-hospital death; secondary outcomes were successful extubation and discharge alive from the hospital. Patients were censored at study day 32 to allow for 30 days of follow-up from the end of the baseline period.

Statistical analysis

Patient characteristics assessed for association with early goal EN and considered for inclusion in models were age, sex, BMI, APACHE II, presence of active infection, use of vasopressors during study days 0–2 (eg, baseline period) and use of neuromuscular blockade during study days 0–2. Means (SD) and counts (percentages) of continuous and categorical patient baseline characteristics, respectively, were tabulated for all patients.

Tests for association between early goal EN and outcomes accounted for 'competing risks' as hospital death and discharge alive are mutually exclusive events. Similarly, we accounted for the competing risk of death in models of successful extubation. Time to event was modelled using the Fine and Gray subdistribution method,[16] which estimates the relative hazards among patients who have not yet experienced the event of interest. A predictor which is significant in this model would, by extension, also be significant and of a corresponding direction in a model of cumulative incidence; these models are thus useful in gauging the impact of a predictor on absolute risk. As advised by Austin *et al*,[17 18] we also present cause-specific hazard models which estimate the impact of the predictor absent other competing risks. We have elected to use these complementary approaches to modelling (with and without the inclusion of competing risks) to be rigorous in our examination of outcomes in our study.

Table 3 Unadjusted and adjusted models for primary and secondary outcomes

Outcome	Model*	HR	P value
In-hospital death	Subdistribution, unadjusted	0.63	0.0003
	Cause-specific, unadjusted	0.74	0.02
	Subdistribution, adjusted	0.73	0.02
	Cause-specific, adjusted	0.81	0.12
Successful extubation	Subdistribution, unadjusted	1.41	<0.0001
	Cause-specific, unadjusted	1.43	<0.0001
	Subdistribution, adjusted	1.27	0.002
	Cause-specific, adjusted	1.28	0.004
Hospital discharge alive	Subdistribution, unadjusted	1.54	<0.0001
	Cause-specific, unadjusted	1.50	<0.0001
	Subdistribution, adjusted	1.24	0.02
	Cause-specific, adjusted	1.23	0.02

*Subdistribution HRs estimate the relative hazards among patients who have not yet experienced the event of interest. Cause-specific HRs estimate hazards only among those who have not experienced any event. Unadjusted tests of associations were run as well as adjusted models which controlled for age, sex, body mass index, Acute Physiology and Chronic Health Evaluation Score, II, presence of active infection, use of vasopressors during study days 0–2 (eg, baseline period) and use of neuromuscular blockade during study days 0–2.

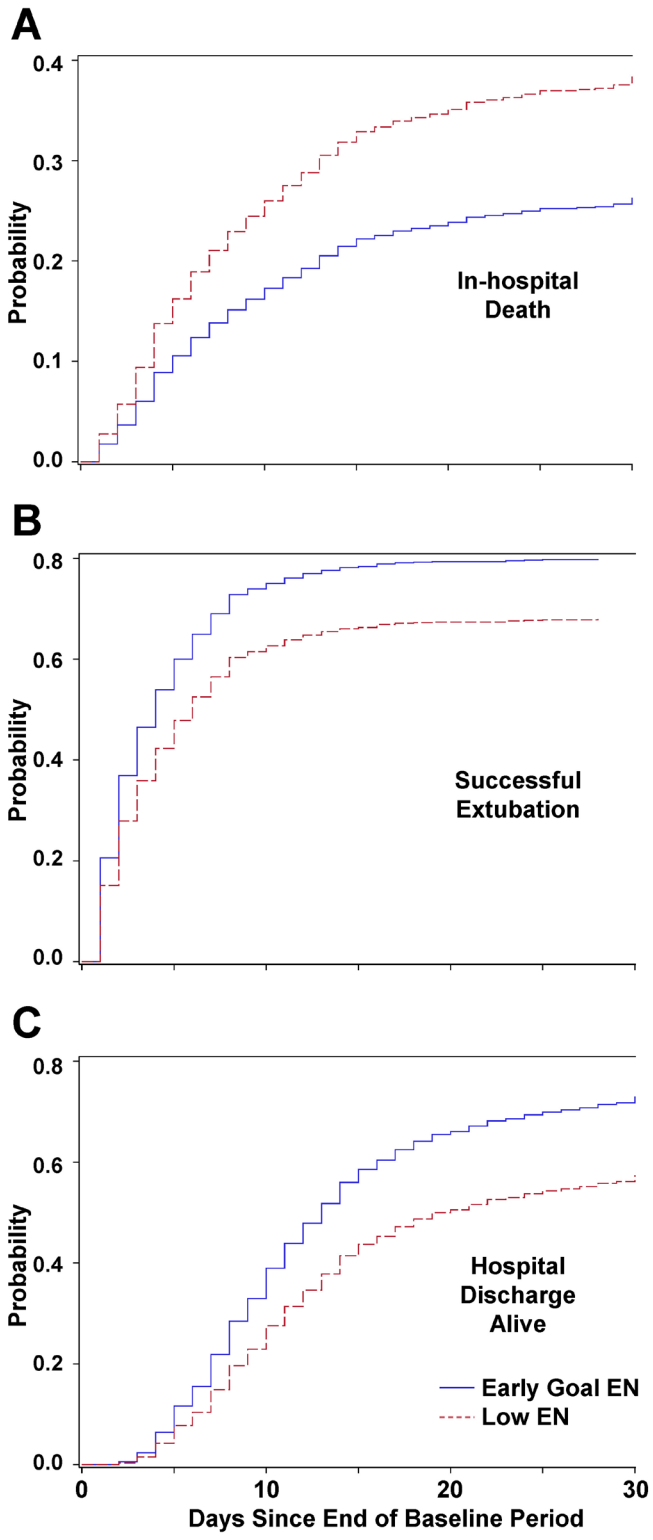

Figure 2 Cumulative incidence of clinical outcomes for early goal EN (blue solid line, ——) and low EN (red dashed line, – – –) groups during the 30 days postbaseline period. (A) In-hospital death, (B) successful extubation and (C) hospital discharge alive. EN, enteral nutrition.

Both unadjusted and adjusted models were run. Covariates controlled for in adjusted models included age, sex, BMI, APACHE II, the presence of active infection, use of vasopressors during study days 0–2 (eg, baseline period) and use of neuromuscular blockade during study days 0–2. In a set of sensitivity analyses, we repeated all survival models with early goal EN defined as achieving 80% of recommended daily calories (instead of 70%) during the baseline period. Analyses were conducted by using SAS V.9.4. Statistical significance was defined as a two-tailed $p<0.05$.

RESULTS

We identified 1366 patients that met inclusion criteria within our two MICU locations. We then excluded patients with missing data, death or extubation during the baseline period (figure 1). This yielded 938 patients in the analytical sample with 306 achieving early goal EN (ie, receipt of at least 70% of recommended daily calories during the baseline period) and 632 who did not. Baseline characteristics and illness severity for all eligible patients are presented in table 1. In the overall cohort, hypertension was the most common comorbidity (68%), followed by diabetes mellitus (40%), chronic obstructive pulmonary disease (29%) and malignancy (25%).

In early goal EN group, the mean proportion of recommended daily calories on the first day postintubation was 0.50±0.32 and 0.94±0.31 on the second day postintubation (ie, at the end of the baseline period). In contrast, in the group which did not achieve early goal EN, the mean proportion of recommended daily calories on the first day postintubation was 0.08±0.15 and 0.22±0.21 on the second day postintubation. In fact, in the full analytical sample, only 64% of patients ever reached 70% of total recommended daily calories within 7 days of intubation. Descriptive data regarding proportion of indicated calories received by patients in each group during the baseline period are included in table 2.

In unadjusted models, early goal EN was associated with a significant decrease in hazard for in-hospital death under both subdistribution and cause-specific hazard models (subdistribution HR (SHR) 0.63, p=0.0003; cause-specific HR (CSHR)=0.74, p=0.02, (table 3)). Similar results were found in adjusted models (SHR=0.73, p=0.02) although the test of association for the cause-specific analyses was only marginally significant (CSHR 0.81, p=0.12).

Regarding secondary outcomes, early goal EN was associated with a significant increase in successful extubation in unadjusted (SHR=1.41, p<0.0001; CSHR=1.43, p<0.0001) and adjusted models (SHR=1.27, p<0.002; CSHR=1.28, p<0.004). Finally, early goal EN was also associated with a significant increase in discharge alive under both analyses and in unadjusted and adjusted models (table 3). Results for the sensitivity analyses with early goal EN alternatively defined as achieving 80% of recommended calories during the baseline period agreed with those reported in table 3; associations between early goal EN and both mortality and discharge alive were slightly stronger and p values were reduced (online supplemental table S.1). Figure 2 plots the cumulative incidence of each outcome for early goal EN

and low EN groups during the 30 days postbaseline period; early feeding is associated with a significant decrease in the cumulative incidence of in-hospital death and a significant increase in the cumulative incidence of both discharge alive and successful extubation.

DISCUSSION

In this large cohort of over 900 critically ill, mechanically ventilated MICU patients, we observed a decrease in death and an increase in successful extubation and discharge alive from the hospital for patients who achieved early goal EN; this finding was robust to adjustment for covariates which also impact death, extubation and discharge. Though the HR for in-hospital death became marginally significant in cause-specific models, a significant test of association in the subdistribution hazard models indicates that a significant test of association of a different magnitude but the same direction would be found for the predictor in models of cumulative incidence of the outcome. We can thus conclude that early feeding is associated with a decreased absolute risk of death and an increased absolute risk of extubation and discharge alive. The decreased impact of feeding in the cause-specific model is likely because the cause-specific model does not account for the competing risk of discharge. We additionally note an overall low delivery of intended calories, with more than half of the patients never achieving 70% of recommended caloric intake within the first 7 days of intubation consistent with many previously described studies observing frequent barriers to reaching recommended EN caloric intake.[7 8]

This retrospective study of a large MICU cohort shows the benefit of achieving 70% or more of the recommended calories within 2 calendar days of intubation. It is a strength of our study that we have included a broad MICU population including patients on vasopressors and neuromuscular blockade. Furthermore, our study reflects 'real-world' titration schedules that can take 24–48 hours to achieve meaningful calorie delivery. There is a notable bimodal pattern between groups in our study; patients achieving early goal EN have much higher calorie intake (eg, mean and median intake equal or greater than 85% on study day 2) vs those who did not achieve early goal EN (eg, mean and median equal or less than 20% of recommended on study day 2). Additionally, we had very few patients in our cohort who approached 100% of recommended feeds during the baseline period when endogenous energy production remained high. These feeding patterns may explain apparently contrasting results in our study versus prior studies which show improved outcomes with 33%–65% of target feeds[9] or studies showing a lack of difference between permissive underfeeding (40%–60% of goal) versus those in the standard feeding group (70%–100% of calculated caloric requirements).[10] These results may further support the hypothesised harms related to both underfeeding and overfeeding during critical illness noted in the introduction.[13] Underfeeding may occur due to slow titration of feeds, interruptions in continuous regimens and/or provider reluctance to feed for a variety of clinical reasons. Overfeeding may occur due to inaccuracies in the measurement of energy needs including underestimation of endogenous energy production in the early days of critical illness.[12]

Limitations

This study was limited by its retrospective observational nature and the inherent bias this introduces. We have considered that feeds are limited in patients with high clinical severity and thus the difference in outcomes may be related to this bias rather than true harm or benefit from the early goal EN. We attempted to limit this confounding via model adjustment. For instance, in adjusted models, we have controlled for APACHE II, presence of infection, use of vasopressors and use of neuromuscular blockade which are all likely to influence the ability to achieve adequate feeding in the baseline period and likely to influence outcomes. Despite such adjustment, we recognise that there may be some residual confounding. Additionally, due to constraints of automated and manual chart review, we did not account for calories obtained from protein supplements or non-nutritional sources (such as dextrose or propofol infusions). Finally, as we were constrained to study the feeding patterns as they occurred in our unit, we could not fully explore the harms and benefits of various feeding doses (eg, moderate doses between 30% and 60% or high doses approaching 100%).

CONCLUSIONS

Early achievement of 70% recommended EN was associated with a reduction of in-hospital death in a mechanically ventilated medically critically ill adult population. Early goal EN was additionally associated with increases in successful extubation and discharge alive. This study supports the need for future investigations that help define optimal dosing and timing of EN during critical illness.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Study procedures were approved by the Yale Institutional Review Board (IRB) and deemed exempt from individual informed consent (HIC # 2000026763, date of approval and exemption determination 30 October 2019). Study procedures were followed in accordance with the ethical standards of the Yale IRB and with the Declaration of Helsinki of 1975.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	6,8
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9 Fig 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	n/a

Outcome data	15*	Report numbers of outcome events or summary measures over time	Fig 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Early Goal Enteral Nutrition Associated with Decreased In-hospital Death in Mechanically Ventilated Critically Ill Adults: Retrospective Cohort Study

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SUPPLEMENTARY MATERIALS

Table S.1: Sensitivity analyses for unadjusted and adjusted models for primary and secondary outcomes with early goal EN defined as achieving 80% or more of recommended daily calories in the baseline period.

Outcome	Model*	Hazard Ratio	p-value
In-hospital death	Subdistribution, unadjusted	0.58	<0.001
	Cause specific, unadjusted	0.68	<0.01
	Subdistribution, adjusted	0.67	<0.01
	Cause specific, adjusted	0.75	0.05
Successful Extubation	Subdistribution, unadjusted	1.36	<0.0001
	Cause specific, unadjusted	1.39	<0.0001
	Subdistribution, adjusted	1.22	0.01
	Cause specific, adjusted	1.24	0.01
Hospital Discharge Alive	Subdistribution, unadjusted	1.57	<0.0001
	Cause specific, unadjusted	1.51	<0.0001
	Subdistribution, adjusted	1.31	<0.01
	Cause specific, adjusted	1.24	0.02

* Subdistribution hazard ratios estimate the relative hazards among patients who have not yet experienced the event of interest. Cause-specific hazard ratios estimate hazards only among those who have not experienced any event. Unadjusted tests of associations were run as well as adjusted models which controlled for age, sex, body mass index, Acute Physiology and Chronic Health Evaluation (APACHE II) Score, II, presence of active infection, use of vasopressors during study day 0 to 2 (e.g., baseline period), and use of neuromuscular blockade during study day 0 to 2,