Effects of Early Enteral Feeding on the Outcome of Critically Ill Mechanically Ventilated Medical Patients*

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Study objectives: **To determine the impact of early enteral feeding on the outcome of critically ill medical patients.**
Design: **Retrospective analysis of a prospectively collected large multi-institutional ICU database.**
Patients: **A total of 4,049 patients requiring mechanical ventilation for > 2 days.**
Measurements and results: **Patients were classified according to whether or not they received enteral feeding within 48 h of mechanical ventilation onset. The 2,537 patients (63%) who did receive enteral feeding were labeled as the "early feeding group," and the remaining 1,512 patients (37%) were labeled as the "late feeding group." The overall ICU and hospital mortality were lower in the early feeding group (18.1% vs 21.4%, p = 0.01; and 28.7% vs 33.5%, p = 0.001, respectively). The lower mortality rates in the early feeding group were most evident in the sickest group as defined by quartiles of severity of illness scores. Three separate models were done using each of the different scores (acute physiology and chronic health evaluation II, simplified acute physiology score II, and mortality prediction model at time 0). In all models, early enteral feeding was associated with an approximately 20% decrease in ICU mortality and a 25% decrease in hospital mortality. We also analyzed the data after controlling for confounding by matching for propensity score. In this analysis, early feeding was again associated with decreased ICU and hospital mortality. In all adjusted analysis, early feeding was found to be independently associated with an increased risk of ventilator-associated pneumonia (VAP) developing.**
Conclusion: **Early feeding significantly reduces ICU and hospital mortality based mainly on improvements in the sickest patients, despite being associated with an increased risk of VAP developing. Routine administration of such therapy in medical patients receiving mechanical ventilation is suggested, especially in patients at high risk of death.**

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Key words: critical care; nutrition; pneumonia; ventilation

Abbreviations: APACHE = acute physiologic and chronic health evaluation; Cox PH = Cox proportional hazard; MPM-0 = mortality prediction model at time 0; SAPS = simplified acute physiology score; VAP = ventilator-associated pneumonia

Nutritional support has evolved as an essential component in the care of critically ill patients. Malnutrition has been associated with poor outcomes among ICU patients, as evidenced by increased morbidity, mortality, and length of stay.[1–10] A growing body of evidence suggests that in the presence of a functional gut, nutrition should be administered through the enteral route largely because of the morbidity associated with other modes of feeding. Favorable effects of enteral feeding include better substrate utilization, prevention of mucosal atrophy, and preservation of gut flora, in-

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tegrity, and immune competence.[11–19] Therefore, there has been an increased interest among physicians to feed patients as soon as possible. Previous studies[20] looking at critically ill patients with abdominal surgery, hip fracture, burn, and trauma demonstrated beneficial effects of early enteral feeding. However, a report[21] from critically ill medical patients suggested that early feeding to satisfy the patient's nutritional needs resulted in more harm and was associated with greater infectious complications. Hence, the optimal timing of enteral feeding in critically ill medical patients is unclear.

We therefore sought to examine the impact of early enteral feeding on ICU and hospital mortality in a large population of critically ill medical patients. Our hypothesis was that a lower mortality would be observed in patients who receive early enteral feeding.

Materials and Methods

Data were obtained from a large, multi-institutional, critical care patient data set (Project Impact Critical Care Data System; Society of Critical Care Medicine; Des Plaines, IL; see www.cerner.com/piccm/ for project details). Dedicated coordinators at each of the participating sites collected the data prospectively from the patient charts. The database was acquired on January 2003, following the approval of the study protocol by the Project Impact Study Committee. The research design was approved by the Institutional Review Board of the Henry Ford Health Sciences Center.

Data were requested on all nonsurgical patients admitted to an ICU who received mechanical ventilation during an ICU stay. Study variables included patient age, gender, race, admitting diagnosis, mortality prediction model at time 0 (MPM-0), simplified acute physiologic score (SAPS) II, and acute physiologic and chronic health evaluation (APACHE) II score. Ventilator-associated pneumonia (VAP) in this database was defined as new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of the following: (1) new onset of purulent sputum or change in character of sputum; (2) organism isolated from blood culture; (3) isolation of pathogen from specimen obtained by tracheal aspirate, bronchial brushing, or biopsy; or (4) histopathologic diagnosis of pneumonia. The primary outcome variables were ICU and hospital mortality. Secondary outcome variables included VAP and ICU length of stay and ventilator-free days. Ventilator-free days were defined as the number of days within the first 28 after initial intubation that the patient was breathing independently of the ventilator. No information allowing identification of the individual patient, hospital, or physician was supplied to the researchers.

The cohort was divided into two groups according to the time of initial start of enteral nutrition. The early feeding group included patients who were started on enteral feeding within 48 h of mechanical ventilation onset. The remainder of the patients comprised the late feeding group. We excluded all patients who died or were extubated within 2 days of initiation of mechanical ventilation. Attempts were made to exclude patients who would have a contraindication to enteral feeding on admission. Thus, patients admitted with GI obstruction or bleed, intestinal ileus, gastroparesis, acute pancreatitis, peritonitis, ischemic colitis, and esophageal rupture were excluded. We also excluded all patients who received total parenteral nutrition prior to mechanical ventilation.

Statistics

Analysis was performed to compare the early and late feeding groups. Baseline characteristics were compared using the Student unpaired *t* test in the case of continuous variables and χ^2 test in case of dichotomous variables. Mortality for each feeding group was calculated according to quartiles of APACHE II, SAPS II, and MPM-0 scores and was compared with the χ^2 test. Survival analysis was done according to the Kaplan-Meier method to assess the impact of early feeding on mortality. In this analysis, the time from mechanical ventilation to death was compared in the two groups using a log-rank test.

Logistic regression was performed to assess the effect of early feeding on ICU and hospital mortality after controlling for important confounders. To control for severity of illness, we developed three separate models using each of the severity of illness scoring systems separately (APACHE II, SAPS II, and MPM-0). In each of these models, we also controlled for age, gender, race, source of admission, and admitting diagnosis as we believed that these variables were important confounders. Thus, they were included in all models regardless of the p value associated with the variable. Odds ratio were computed from the coefficients in the logistic model, and 95% confidence intervals were calculated for all variables. An α level of < 0.05 was considered indicative of statistical significance. To assess the effect of feeding on the risk of death, we performed Cox proportional hazard (Cox PH) analyses. Again, we constructed three different models with each of the severity scores and controlled for all of the variables included in the logistic regression.

Logistic regressions were also done to assess the effect of early feeding on VAP. In these analyses, the models also included the use of drugs that may have confounded the analysis. Specifically, use of histamine type-2 blockers, proton pump inhibitors, narcotics, and paralytic agents were included in the models.

Matching by Propensity Score

As in any nonrandomized study, there was a possibility in our study that there were inherent differences between the two groups. To control for this, we did analyses to specifically control for potential confounding variables (see above). However, even with these methods, it is possible that residual bias may exist. To control for such biases, propensity score methods have been proposed.[22–24] By using propensity scores, one can better control for the likelihood of being assigned to a group.

In our study, we modeled the likelihood of being fed early using logistic regression. We included the severity of illness (SAPS II score), age, sex, site of origin, and APACHE II admitting diagnosis group in our regression. This analysis allowed us to calculate a probability of being fed for each patient. We then performed matching according to the procedure described by Connors et al[25] using a Statistical Analysis Software (SAS Institute; Cary, NC) macro described by Parsons.[26] Basically, a randomly selected patient who was fed was selected from the population. Then, all of the patients who were not fed early were searched to find a match on the propensity score (within 0.01 on a scale from 0 to 1). This was continued until all possible pairs were identified. The success of this matching was assessed by evaluating differences in individual demographic data (Table 1).

After matching was completed, the new matched data set was evaluated to assess the effect of feeding on ICU mortality,

Table 1—*Baseline Characteristics of the Matched Study Population (n = 2,528)**

Characteristics	Early Feeding Group (n = 1,264)	Late Feeding Group (n = 1,264)	p Value
Mean age, yr	59.8 ± 17.5	59.6 ± 18.1	0.76
Sex			
Male	693 (54.8)	676 (53.5)	0.49
Female	571 (45.2)	588 (46.5)	
Race			
White	975 (78.0)	943 (75.3)	0.30
African American	210 (16.8)	238 (19.0)	
Hispanic	41 (3.3)	50 (4.0)	
Other	24 (1.9)	22 (1.8)	
Admission source			
Outpatient	810 (64.3)	779 (62.2)	0.49
General care floor	359 (28.5)	379 (30.3)	
Another ICU	68 (5.4)	76 (6.1)	
Extended care facility	23 (1.8)	19 (1.5)	
Reason for ICU admission			
Respiratory	592 (46.8)	618 (48.9)	0.29
Sepsis	127 (10.1)	114 (9.0)	
Cardiac	119 (9.4)	130 (10.3)	
CNS disorder	232 (18.4)	223 (17.6)	
Others	194 (15.4)	179 (14.2)	
Severity scores			
APACHE II	20.7 ± 7.1	20.9 ± 7.9	0.45
MPM-0	0.32 ± 0.23	0.33 ± 0.24	0.19
SAPS II	46.9 ± 15.4	46.8 ± 16.0	0.94

*Data are presented as No. (%) or mean ± SD.

hospital mortality, ICU length of stay, length of ventilation, and VAP. All of these analyses were done using methods that accounted for the matched design. Thus, continuous variables were compared using a matched *t* test (Proc Mixed in SAS; SAS Institute), and dichotomous outcomes were compared using conditional logistic regression (Proc Phreg in SAS; SAS Institute). Kaplan-Meier survival analyses were done without accounting for matching; however, survival was also analyzed using Cox proportional hazard methods while accounting for matching. All statistical analysis was done using statistical software (SAS version 9.1; SAS Institute).

RESULTS

Patients

At the time of the query, a total of 4,786 patients met our inclusion criteria in the Project Impact Database. Of those, 393 were excluded because they received mechanical ventilation for < 2 days, 325 patients were excluded because they were not eligible for early enteral feeding due to GI complications, and 19 patients were excluded because they received total parenteral nutrition prior to mechanical ventilation onset. Therefore, a total 4,049 patients were included in the study, of whom 2,537 patients (63%) received early enteral feeding and 1,512 patients (37%) did not. At least one severity of illness score was available in each of these patients (APACHE II, 3,247 records [55.5%]; SAPS II, 3,742 records [92.4%]; and MPM-0, 3,645 records [90.0%]). The mean APACHE II, SAPS II, and MPM-0 scores were 20.7 ± 7.4, 46.4 ± 15.4 and 0.32 ± 0.23, respectively (± SD).

At baseline, significant differences in patient characteristics were found between the two study groups (Table 2). Patients in the early feeding group were older in age and included a higher proportion of white patients compared to the late feeding group. Additionally, the early feeding group had a lower severity of illness as shown by the MPM-0 and SAPS II scores, but not APACHE II.

Mortality Analysis

Patients in the early feeding group had a lower ICU and hospital mortality in an unadjusted analysis (18.1% vs 21.4%, p = 0.01; and 28.7% vs 33.5%, p = 0.001, respectively) [Table 3]. The mortality data as analyzed by quartiles of severity scores for each feeding group are summarized in Figures 1–3 2. No statistically significant differences in ICU and hospital mortality were observed in the first three quartiles of APACHE II, SAPS II, and MPM-0 scores between the two feeding groups. In the fourth quartile (*ie*, APACHE II ≥ 25, SAPS II ≥ 56, and

Table 2—*Baseline Characteristics of the Study Population (n = 4,049)**

Characteristics	Early Feeding Group (n = 2,537)	Late Feeding Group (n = 1,512)	p Value
Mean age, yr	62.3 ± 16.7	60.1 ± 18.3	0.0001
Sex			
Male	1,370 (54.0)	1,166 (46.0)	0.8
Female	820 (54.3)	691 (45.7)	
Race			
White	2,009 (80.0)	1,138 (76.1)	0.01
African American	380 (15.1)	276 (18.5)	
Hispanic	79 (3.2)	57 (3.8)	
Other	43 (1.7)	24 (1.6)	
Admission source			
Outpatient	1,404 (55.7)	937 (62.6)	0.001
General care floor	852 (33.8)	448 (29.9)	
Another ICU	221 (8.8)	89 (6.0)	
Extended care facility	45 (1.8)	23 (1.5)	
Reason for ICU admission			
Respiratory	1,486 (58.6)	653 (43.2)	0.0001
Sepsis	184 (7.3)	133 (8.8)	
Cardiac	201 (7.9)	276 (18.3)	
CNS disorder	404 (15.9)	235 (15.5)	
Others	262 (10.3)	215 (14.2)	
Severity scores			
APACHE II	20.6 ± 7.0	21.0 ± 8.0	0.1
MPM-0	0.32 ± 0.22	0.34 ± 0.25	0.004
SAPS II	45.9 ± 14.9	47.3 ± 16.2	0.01

*Data are presented as No. (%) or mean ± SD.

Table 3—*Comparison of Clinical Outcomes in Early and Late Feeding Groups**

Characteristics	Early Feeding Group (n = 2,537)	Late Feeding Group (n = 1,512)	p Value
ICU mortality	458 (18.1)	323 (21.4)	0.01
Hospital mortality	727 (28.7)	511 (33.9)	0.001
VAP	284 (11.2)	143 (9.5)	0.08
ICU length of stay, d	10.9 ± 8.1	10.2 ± 7.7	0.01
Ventilator-free days, No.†	17.0 ± 9.0	16.8 ± 9.9	0.54

*Data are presented as No. (%) or mean ± SD.

†Ventilator-free days are the number of days (among the first 28 days after intubation) that the patient spends breathing independently of the ventilator.

MPM-0 probability of survival < 0.54), there was a significant decrease in ICU and hospital mortality in the early feeding group ($p < 0.05$). To evaluate the independent effect of feeding on ICU and hospital mortality, we constructed three different multivariate logistic models for each of the severity scores. This analysis revealed that regardless of the severity score used, early feeding was consistently associated with a lower risk of ICU and hospital mortality (Table 4). Age, severity of illness and admission from an inpatient unit were found to be significant predictors of ICU and hospital mortality in these analyses. To assess the effect of early feeding on survival and the risk of death, we performed Kaplan-Meier analysis as well as Cox PH analysis. The Kaplan-Meier analysis of survival showed that there was a significant improvement in survival for the patients fed early (p = 0.0005) [Fig 4]. The absolute difference in survival between the two groups was evident within the first week of mechanical ventilation and remained constant throughout the first 28 days of postintubation ICU follow-up. The Cox PH analyses showed that after correcting for confounders, early feeding was associated with an approximately 20% decreased risk of death (Table 4).

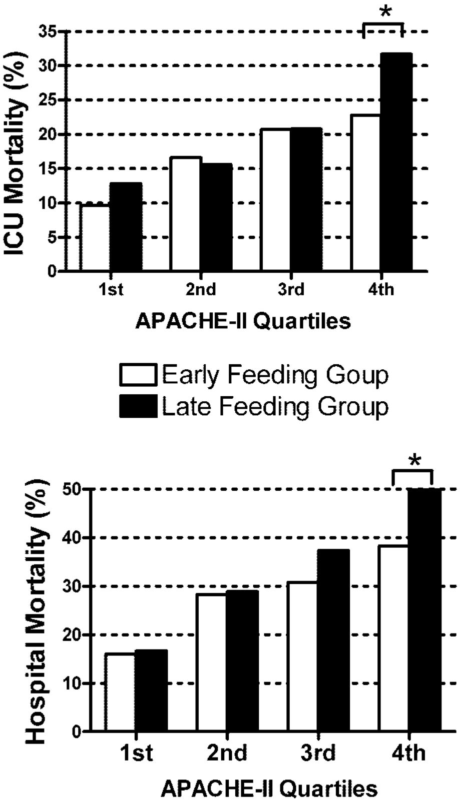

FIGURE 1. ICU and hospital mortality according to APACHE II quartiles. For patients who received early feeding, there is a significant decrease in ICU and hospital mortality detected in the fourth APACHE II quartile (*$p < 0.05$).

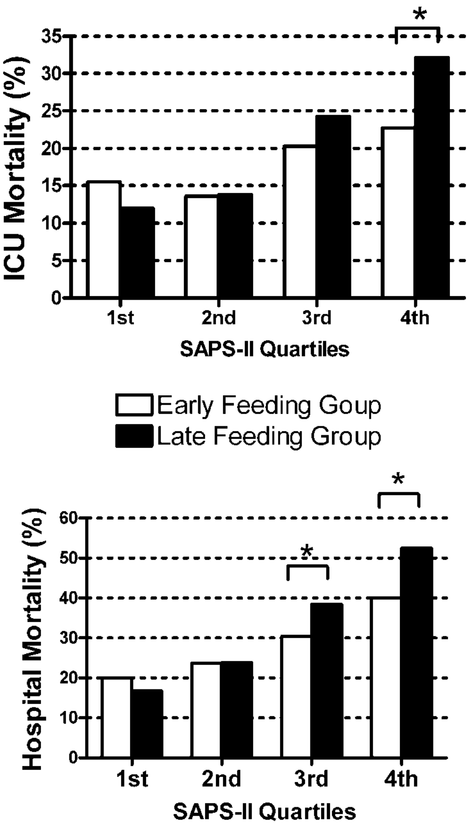

FIGURE 2. ICU and hospital mortality according to SAPS II quartiles. For patients who received early feeding, there is a significant decrease in ICU and hospital mortality detected in the fourth SAPS II quartile (*$p < 0.05$). There is also a decreased mortality in the third quartile of SAPS II scores for hospital mortality.

VAP

In an unadjusted analysis, there was no significant difference in the development of VAP among the early feeding and the late feeding groups (11.2% vs 9.5%, p = 0.08) [Table 3]. However, early feeding

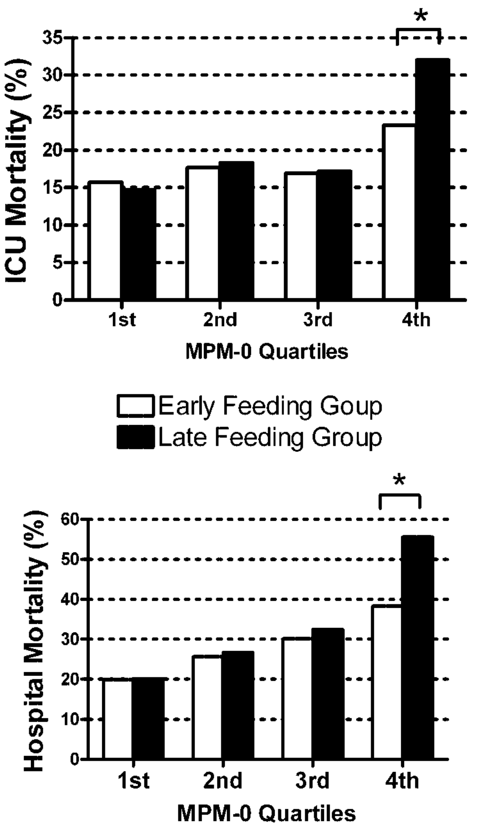

FIGURE 3. ICU and hospital mortality according to MPM-0 quartiles. For patients who received early feeding, there is a significant decrease in ICU and hospital mortality detected in the fourth MPM-0 quartile (*$p < 0.05$).

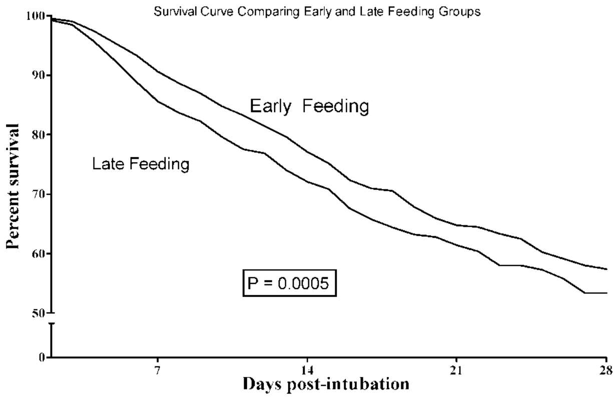

FIGURE 4. Kaplan-Meier estimates of survival among 2,537 critically ill medical patients in early feeding group and 1,512 patients in the late feeding group. Early feeding was associated with a significantly higher rate of survival ($p = 0.0005$ by the log-rank test).

was associated with increased risk of VAP in APACHE II–, SAPS II–, and MPM-0–adjusted analyses (Table 4). Age, male sex, and admission from another ICU were also found to be independent predictors of VAP in the models (data not shown). This increase in VAP rates did not result in an overall decrease in ventilator-free days (Table 3).

Matched Analysis

As described in the methods, we developed a propensity score for the likelihood of being fed using logistic regression. We then performed matching for this score and found 1,264 pairs of patients who were within 0.01 points on this score. Matching on this score allowed us to find two well-matched groups as shown in Table 1. There were no significant differences on any of the baseline values tested. Using this well-matched subgroup of patients, we again found significant differences in outcomes. Patients in the early feeding group had a lower ICU and hospital mortality (17.6% vs 21.3%, $p = 0.02$; and 27.8% vs 34.2%, $p = 0.0005$, respectively) [Table 5]. This was true despite the fact that early feeding was associated with an increased risk of VAP (Table 5). The difference in survival can also be seen in the Kaplan-Meier survival curve (Fig 5). As this analysis could not be done while accounting for the matched design, we did a Cox PH analysis after accounting for matching. This analysis showed that being fed early was associated with a 30% decreased risk of death (odds ratio, 0.70; 95% confidence interval, 0.55 to 0.90; $p = 0.005$).

DISCUSSION

In this study, administration of enteral feeding within 48 h of mechanical ventilation reduced the rates of ICU and hospital mortality in a large cohort

Table 4—*Outcomes in Association with Early Enteral Feeding**

Severity Scores	ICU Mortality	Hospital Mortality	VAP	Risk of Death by Cox PH Model
APACHE II	0.80 (0.66–0.97)	0.73 (0.62–0.87)	1.34 (1.04–1.73)	0.79 (0.67–0.94)
SAPS II	0.80 (0.67–0.96)	0.73 (0.62–0.85)	1.41 (1.41–1.78)	0.80 (0.69–0.93)
MPM-0	0.82 (0.69–0.98)	0.73 (0.62–0.85)	1.41 (1.11–1.80)	0.82 (0.70–0.96)

*Data are presented as odds ratio (95% confidence interval). Results of the different multivariable models adjusting for each of the severity of illness scores as well as age, gender, race, source of admission, and admitting diagnosis.

Table 5—*Comparison of Clinical Outcomes in Early and Late Feeding Groups After Matching for Propensity Score**

Characteristics	Early Feeding Group (n = 1,264)	Late Feeding Group (n = 1,264)	p Value
ICU mortality	222 (17.6)	268 (21.3)	0.02
Hospital mortality	349 (27.8)	431 (34.2)	0.0005
VAP	163 (12.9)	120 (9.5)	0.007
ICU length of stay, d	11.2 ± 8.2	10.4 ± 8.0	0.006
Ventilator-free days, No.†	16.8 ± 8.9	16.8 ± 9.9	0.84

*Data are presented as No. (%) or mean ± SD.

†Ventilator-free days are the number of days (among the first 28 days after intubation) that the patient spends breathing independently of the ventilator.

of critically ill patients receiving mechanical ventilation. This large sample drawn from various ICUs around the country provides a reflection of physicians' practices in regards to nutritional supplementation in critically ill medical patients. There is a higher tendency among physicians to provide early feeding for patients who are older, white, and with a lower severity of illness. In addition, patients admitted with respiratory diagnoses are more likely to receive feeding earlier than those admitted with cardiac diagnoses. Despite the heterogeneity of the population, a consistent effect of early feeding was seen after adjusting for various confounders, and this benefit was most apparent in patients with higher severity of illness. The effect was also seen in a subgroup that was well matched using a propensity score method.

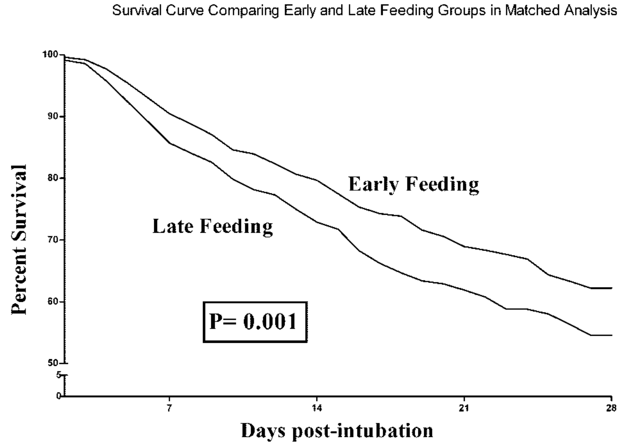

FIGURE 5. Kaplan-Meier estimates of survival among 1,264 critically ill medical patients in early feeding group and 1,264 patients in the late feeding group. The two groups were matched according to the likelihood they would be fed by using a propensity score. Early feeding was associated with a significantly higher rate of survival (p = 0.001 by the log-rank test).

Prior research has shown the advantages of early enteral feeding.[20] Experimental studies[13,27–30] on burn animals showed that immediate enteral feeding was associated with a decrease in the hypermetabolic state, suppression of the catabolic hormones, and less bacterial translocation from the intestinal tract. Human studies investigating the effects of early feeding included relatively small number of patients, focused primarily on surgical and trauma patients, and used different feeding formulas including those with immune-enhancing properties. A metaanalysis[20] of these studies showed that early enteral feeding was associated with a significantly lower incidence of infections and reduced length of hospital stay, but there was no demonstrable difference in mortality. Thus, research in surgical patients has shown many benefits of early feeding but failed to prove that this practice decreased mortality.

Studies in medical patients have directly contradicted the benefits seen in surgical patients. To date, the only study comparing early and late enteral feeding in medical ICU patients receiving mechanical ventilation was conducted by Ibrahim and colleagues.[21] The study protocol was that patients either received enteral nutrition to satisfy their nutritional requirements from day 1 (early feeding group), or they received only 20% of their requirements for the first 4 days of their ICU stay (late feeding group). In that study, there was no mortality difference between the early and late enteral feeding groups. However, the group of patients who were fed earlier had a greater incidence of VAP and longer ICU stay. These results challenged the concept that early feeding was beneficial. Thus, it was recognized that further research was required to assess the effect of early feeding in medical patients.

In our study, adjusted analysis demonstrated an increased risk of VAP associated with early enteral feeding. Nevertheless, this did not translate into an increased risk of death. The favorable effects of early enteral feeding in patients with lower disease severity offset the increased mortality rate often associated with VAP. In the more critically ill patients, the benefits of early enteral nutrition outweighed and overshadowed the detrimental effects of increased VAP rates, resulting in a significant survival advantage. Despite the increased VAP rate, our results support the use of early enteral feeding in medical ICU patients due to the advantage in mortality outcome, more clearly seen in the sickest patients.

Findings from the current investigation should be interpreted with caution. The results of our study were based on intent-to-treat analysis (*ie*, whether or not patients were initiated on feeding within 48 h of mechanical ventilation). It is well known that critically ill patients have frequent interruptions of enteral feeds for various reasons and most do not reach their nutritional goals.[31] Our database did not have information pertaining to nutritional goals, rate of advancement or disruption of the enteral feeding. The impact of this limitation on our results is difficult to predict, and the relationship between the level of caloric intake and clinical outcomes of critically ill patients remains controversial.[32,33] In any case, our data speaks in favor of the intent to provide early enteral feeding.

The question of "how early is early?" is important because administration of early feeding requires time and dedication. In our study, early feeding was arbitrarily defined as intent to feed within 2 days of mechanical ventilation. In a separate analysis using a 24-h limit for early feeding, the results of our study remained unchanged (Table 6). This suggests that earlier is probably at least as good. Other questions such as "how much to feed" and "how fast to advance" remain controversial, and this current study was not designed to detect these factors.

Our study has other limitations. First, the database does not include information on the route of feeding, specifically whether it was gastric or postpyloric. Studies[34,35] comparing the two routes of enteral feeding had conflicting results. A metaanalysis[36] did not find any clinical advantage from postpyloric feeding, and showed similar rates of pneumonia, ICU length of stay, and mortality in both feeding groups. Thus, we believe that the effect of this limitation on the results of our study is minimal.

Second, we do not have information regarding the various enteral formulas that patients received, mainly whether they received immune-enhancing nutrition vs standard formula. We doubt that such information would have affected our results. Many studies were conducted to check for benefits of immune-enhancing formulas in a variety of patient groups. A systematic review and consensus statement[37] concluded that immune-enhancing diets may offer advantages in critically ill patients; specifically, the authors concluded that immunonutrition could be offered to specific patient groups with the goals of reducing certain infections and decreasing ventilator days and ICU length of stay. However, there was no evidence that there was a mortality advantage in any patient group. Thus, our findings are not likely to have been directly impacted by varying use of specific types of nutrition. Third, VAP is often a controversial diagnosis, and without an optimal confirmatory method and its incidence varies considerably depending on the definition used for diagnosis.[38] Hence, the accuracy of data obtained on VAP is a significant concern, and some impact due to misdiagnosis while abstracting this outcome cannot be excluded.

Another concern is confounding by indication. It is possible that practitioners would be less likely to feed more severely ill patients; in other words, the decision to feed patients was not done randomly. Thus, feeding may simply be a marker of a less ill patient rather than an independent factor affecting outcome. We attempted to control for this by using multivariable analysis that included severity of illness measures. We also excluded all patients with an obvious contraindication to feeding. We also used propensity score matching as has been done in other studies.[25] Even with these methods, we cannot control for variables that were not measured. These unmeasured variables may have provided residual confounding. We believe that differences in mortality are too large to be accounted for solely by confounding by indication. Thus we feel that this residual confounding effect, if present, is too small to account for the early feeding mortality benefit. Overcoming this confounder would require a prospective study with a large number of patients. We do believe that given the large difference in mortality seen in this study, that a randomized trial of early feeding in intubated patients should be considered. We can use the ICU and hospital mortalities found in our study to calculate sample size necessary for such a trial to have 80% power. If the trial used ICU mortality as an outcome, such a trial would require 4,688 subjects. If hospital mortality was the outcome, the study would require 2,570 subjects. As these numbers are likely unrealistic, one could instead propose to study only the sickest patients as identified in our study. Depending on the mortality prediction model used, such a study would require between 744 and 972 subjects if ICU mortality was the end point and between 284 and 614 patients if hospital mortality was the outcome. In the absence of such data, our study remains the best evidence to date that early feeding decreases mortality in intubated patients.

This study of early vs late enteral feeding shows

Table 6—*Comparison of Clinical Outcomes in Early and Late Feeding Groups Defining Early Feeding as Within 24 h***

Characteristics	Early Feeding Group (n = 1,865)	Late Feeding Group (n = 2184)	p Value
ICU mortality	333 (17.9)	448 (20.5)	0.03
Hospital mortality	517 (27.8)	721 (33.1)	0.0003
VAP	188 (10.1)	239 (10.9)	0.37
ICU length of stay, d	10.7 ± 8.3	10.6 ± 7.7	0.75
Ventilator-free days, No.†	17.2 ± 9.0	16.8 ± 9.6	0.17

*Data are presented as No. (%) or mean ± SD.

†Ventilator-free days are the number of days (among the first 28 days after intubation) that the patient spends breathing independently of the ventilator.

that early enteral feeding reduces the mortality of critically ill medical patients receiving mechanical ventilation. In subgroup analysis, this benefit seems to be limited to the sickest group of patients. As we have no evidence that feeding is harmful in other subgroups, we would tend to believe that it should be provided for all patients. Nevertheless, our data allow us to only conclude that the administration of early enteral feeding in patients at high risk of death is likely to be beneficial.

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