



The Association between Early Enteral Nutrition and Patient Mortality in the ICU : A Systematic Review

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ABSTRACT

Introduction: Early enteral nutrition (EEN) is recommended in critical care, yet its association with mortality remains debated due to heterogeneous evidence across populations and comparators. This systematic review aims to evaluate the association between EEN and mortality in adult ICU patients, identify condition-specific effects, and determine factors modifying this relationship. **Methods:** A systematic review was conducted on 80 studies including randomized controlled trials, etc examining EEN (initiation within 24-48 hours of ICU admission) compared with delayed EN, parenteral nutrition (PN), or standard care in adult ICU patients. Mortality outcomes were extracted alongside population characteristics, comparators, and effect modifiers. **Results:** In general ICU populations, large RCTs (CALORIES, n=2400; NUTRIREA-2, n=2410) found no mortality difference between early EN and early PN (RR 0.97, p=0.57; 37% vs 35%, p=0.33). However, meta-analyses comparing EEN specifically against delayed EN demonstrated significant mortality reduction (OR 0.45, 95% CI 0.21-0.95,

p=0.038). Condition-specific benefits emerged: sepsis (OR 0.59, 95% CI 0.37-0.94, p=0.03), burns (OR 0.36, 95% CI 0.18-0.72, p=0.003), traumatic brain injury (RR 0.35, 95% CI 0.24-0.50), and severe acute pancreatitis (aOR 0.44, 95% CI 0.20-0.96). Hemodynamic status significantly modified effects: EEN benefited patients with transient or low-to-moderate vasopressor requirements but not those with persistent severe shock (OR 1.28, p=0.485). Methodological quality assessment revealed that positive findings were predominantly from smaller, higher-bias trials. **Discussion:** The mortality association with EEN is comparator-dependent and population-specific. When compared with early PN, EEN shows no survival advantage, indicating the route of early nutrition is less critical than timely nutritional delivery. Conversely, EEN reduces mortality compared with delayed EN, supporting early initiation over delayed strategies. Biological plausibility is supported by immune modulation (Th17/Treg regulation), reduced infectious complications, and gut barrier preservation. Hemodynamic stability represents a critical treatment effect modifier, with benefits confined to resolving or moderate shock. **Conclusion:** EEN is associated with reduced mortality compared to delayed EN in specific ICU populations including sepsis, burns, traumatic brain injury, and severe acute pancreatitis, but not when compared with early PN in general ICU populations. Hemodynamic status should guide clinical decision-making. Future research should prioritize large, low-bias trials in stratified populations.

Keywords: early enteral nutrition, ICU mortality, critical illness, sepsis, traumatic brain injury, burns, acute pancreatitis, hemodynamic stability

INTRODUCTION

Background

Nutritional support in critically ill patients has evolved from an adjunctive therapy to a fundamental component of intensive care unit (ICU) management. Enteral nutrition (EN), particularly when initiated early, is theorized to preserve gut barrier function, modulate immune responses, and reduce infectious complications compared to parenteral nutrition (PN) or delayed feeding strategies (1). The concept of "early" enteral nutrition (EEN) typically refers to initiation within 24-48 hours of ICU admission, injury, or intubation, aligning with international guideline recommendations (2). However, despite widespread adoption, the survival benefit of EEN remains a subject of ongoing debate, with conflicting evidence emerging from large randomized controlled trials and meta-analyses over the past two decades (3-5).

Problem Statement

The critical care community faces a clinical dilemma: while physiological rationale supports early enteral feeding, high-quality evidence demonstrating mortality reduction is inconsistent. The largest trials comparing early EN with early PN—CALORIES (n=2400) and NUTRIREA-2 (n=2410)—found no significant mortality differences, challenging the assumption that enteral route superiority translates to survival advantage (1,2). Conversely, meta-analyses restricted to comparisons against delayed EN suggest significant mortality benefits, particularly in specific subpopulations (4,6). This paradox creates uncertainty for clinicians making real-time decisions about nutritional initiation timing and route in heterogeneous ICU populations with varying diagnoses, illness severities, and hemodynamic statuses.

Research Gap

Previous systematic reviews have either pooled heterogeneous populations without adequately considering comparator type, focused on single disease conditions, or failed to account for effect modifiers such as hemodynamic status and study quality (8,11,13). The landmark trials comparing EN versus PN have been misinterpreted as evidence against EEN, when in fact they

compared two early feeding strategies rather than early versus delayed enteral intake. Furthermore, the differential effects across specific conditions (sepsis, burns, traumatic brain injury, acute pancreatitis) have not been systematically synthesized with attention to the comparator used. Critically, the role of hemodynamic stability as an effect modifier—distinguishing between transient and persistent shock, and between low-dose and high-dose vasopressor requirements—has only recently emerged as a crucial consideration (9,10,19). A comprehensive synthesis that integrates these dimensions is needed to resolve apparent contradictions and guide clinical practice.

Study Objectives

This systematic review aims to:

1. Evaluate the association between early enteral nutrition and mortality in adult ICU patients across different comparator groups (delayed EN, early PN, standard care)
2. Identify condition-specific mortality effects in sepsis, burns, traumatic brain injury, acute pancreatitis, COVID-19, and other critical illnesses
3. Determine patient and study characteristics that modify the EEN-mortality association, particularly hemodynamic status and illness severity
4. Assess the methodological quality of existing evidence and its impact on reported mortality findings
5. Synthesize mechanistic pathways explaining differential treatment effects

Research Hypotheses

Based on the preliminary evidence, we hypothesize that:

1. EEN is associated with reduced mortality when compared specifically against delayed EN, but not when compared against early PN
2. The mortality benefit of EEN is more pronounced in specific conditions characterized by hypermetabolism and gut barrier compromise (burns, traumatic brain injury, sepsis)

3. Hemodynamic status significantly modifies the EEN-mortality association, with benefit confined to patients with transient or resolving shock
4. Study quality substantially influences reported effect sizes, with higher-bias trials overestimating mortality benefits

Significance and Novelty

This review provides several novel contributions to the existing literature. First, it explicitly disentangles the comparator-dependent nature of EEN's mortality association, resolving the apparent contradiction between large RCTs and meta-analyses. Second, it integrates recent evidence on hemodynamic effect modification from large database studies and secondary analyses of RCTs (9,10), offering practical guidance for clinicians managing patients on vasopressors. Third, it synthesizes mechanistic evidence linking EEN to immune modulation (Th17/Treg regulation, IL-23/IL-17 axis) and reduced persistent inflammation-immunosuppression-catabolism syndrome (PICS) (34,43,45). Fourth, it provides condition-specific effect estimates that can inform tailored nutritional strategies. Finally, by incorporating quality assessment and bias analysis, it offers a nuanced interpretation of the evidence hierarchy, distinguishing between signals from high-quality RCTs and potentially inflated effects from smaller studies.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Association between Early Enteral Nutrition and Patient Mortality in the ICU.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age:** Does the study include adult patients (≥ 18 years) admitted to intensive care units?
- **Intervention Timing:** Does the study examine early enteral nutrition initiation (within 24-48 hours of ICU admission or intubation)?
- **Comparison Groups:** Does the study compare early enteral nutrition to delayed enteral nutrition, parenteral nutrition, or standard nutritional care?
- **Mortality Outcomes:** Does the study report mortality as a primary or secondary outcome (ICU mortality, hospital mortality, 28-day mortality, or other defined mortality endpoints)?
- **Study Design:** Is the study design a randomized controlled trial, cohort study, case-control study, systematic review, or meta-analysis?
- **Timing Clarity:** Can the timing of enteral nutrition initiation be clearly determined or defined from the study?
- **Focus on Timing:** Does the study address timing of nutrition initiation (rather than focusing solely on specific nutritional formulations without addressing timing)?
- **Study Type Quality:** Is the study a full research article (not a case report, case series, editorial, or conference abstract)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	ICU Patients	Early Enteral Nutrition	Comparison Groups	Mortality

Keyword 2	Critically Ill Patients	Early Enteral Feeding	Late Enteral Feeding	Survival Rate
Keyword 3	ICU Patients	Optimal Timing	Total Parenteral Nutrition	Prognosis
Keyword 4	Critical Care	Enteral Feeding Protocol	No Enteral Nutrition	In-hospital Mortality

The Boolean MeSH keywords inputted on databases for this research are: (*"ICU Patients" OR "Critically Ill Patients" OR "Critical Care"*) AND (*"Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol"*) AND (*"Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition"*) AND (*"Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality"*)

Data extraction

- **Early EN Definition:**

Extract how early enteral nutrition is defined and implemented in this study, including:

- Timing threshold for 'early' (e.g., within 24 hours, 48 hours of ICU admission)
- Type of enteral nutrition provided (standard formula, immune-enhanced, etc.)
- Route of administration (nasogastric, jejunostomy, etc.)
- Target caloric/protein goals if specified
- Any specific protocols or criteria for initiating early EN

- **ICU Population:**

Extract characteristics of the ICU patient population studied, including:

- Type of ICU patients (medical, surgical, trauma, mixed)

- Specific conditions or diagnoses (COVID-19, post-operative, burn, head injury, etc.)
- Illness severity indicators (APACHE scores, SOFA scores, vasopressor use, mechanical ventilation requirements)
- Sample size and key demographics (age, gender)
- Inclusion and exclusion criteria relevant to ICU status

- **Comparison Group:**

Extract details about what early enteral nutrition was compared against, including:

- Type of comparison (delayed enteral nutrition, parenteral nutrition, standard care, no nutrition)
- Timing of comparison intervention (when delayed EN was started, duration of parenteral nutrition, etc.)
- Any crossover between groups or protocol violations
- Sample size of comparison group

- **Mortality Assessment:**

Extract all mortality outcomes and results for the association between early EN and patient death in ICU patients, including:

- Type of mortality measured (ICU mortality, hospital mortality, 28-day mortality, etc.)
- Timing of mortality assessment
- Raw mortality rates or percentages for early EN vs comparison groups

- Effect measures (odds ratio, relative risk, hazard ratio) with confidence intervals
- Statistical significance (p-values)
- Any adjustment for confounders in mortality analysis

- **Effect Modifiers:**

Extract patient or study characteristics that modify the association between early enteral nutrition and mortality in ICU patients, including:

- Subgroup analyses by patient severity (high vs low APACHE, vasopressor use, etc.)
- Differences by ICU type or patient condition
- Time-dependent effects or optimal timing windows
- Factors that enhanced or diminished the mortality benefit
- Any barriers to early EN implementation that affected outcomes
- Dose-response relationships if analyzed

- **Study Design:**

Extract key methodological features that affect the reliability of the mortality association findings, including:

- Study design (RCT, cohort, before-after, etc.)
- Randomization and allocation concealment methods
- Blinding procedures
- Sample size and power calculations

- Length of follow-up for mortality
- Intention-to-treat vs per-protocol analysis
- Loss to follow-up rates
- Major methodological limitations acknowledged by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("ICU Patients" OR "Critically Ill Patients" OR "Critical Care") AND ("Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol") AND ("Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition") AND ("Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality")</i>	10
Semantic Scholar	<i>("ICU Patients" OR "Critically Ill Patients" OR "Critical Care") AND ("Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol") AND ("Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition") AND ("Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality")</i>	266
Springer	<i>("ICU Patients" OR "Critically Ill Patients" OR "Critical Care") AND ("Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol") AND ("Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition") AND ("Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality")</i>	634
Google Scholar	<i>("ICU Patients" OR "Critically Ill Patients" OR "Critical Care") AND ("Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol") AND ("Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition") AND ("Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality")</i>	5,220
Wiley Online Library	<i>("ICU Patients" OR "Critically Ill Patients" OR "Critical Care") AND ("Early Enteral Nutrition" OR "Early Enteral Feeding" OR "Optimal Timing" OR "Enteral Feeding Protocol") AND ("Comparison Groups" OR "Late Enteral Feeding" OR "Total Parenteral Nutrition" OR "No Enteral Nutrition") AND ("Mortality" OR "Survival Rate" OR "Prognosis" OR "In-hospital Mortality")</i>	506

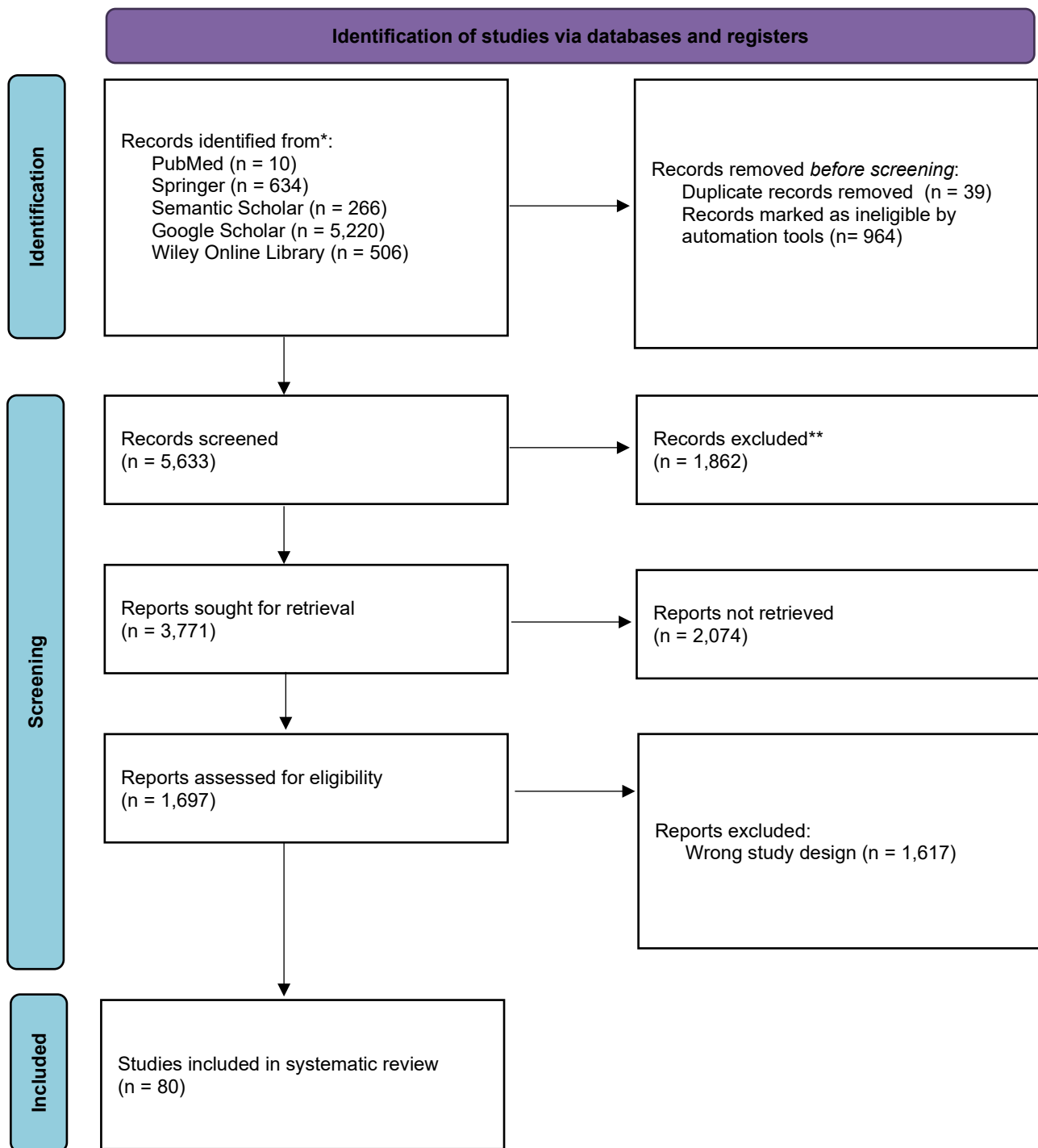


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This review encompasses 80 sources examining the association between early enteral nutrition (EEN) and mortality in ICU patients. The included studies span multiple study designs: randomized controlled trials, retrospective and prospective observational studies, etc. Populations studied include general critically ill patients, those with sepsis or septic shock, traumatic brain injury, burns, acute pancreatitis, ARDS, COVID-19, cardiovascular surgery, and other specific conditions. The definition of "early" enteral nutrition varied across studies, most commonly defined as initiation within 24 to 48 hours of ICU admission, injury, or intubation. Comparators included delayed enteral nutrition, parenteral nutrition, standard care, or no nutrition.

Study	Population	EEN Definition	Comparator	Sample Size
J. Reignier et al., 2018	Ventilated adults with shock [2]	Within 24 h of intubation [2]	Parenteral nutrition [2]	2410 [2]
Feng Tian et al., 2018	Critically ill adults [4]	Within 24 h of ICU admission [4]	Delayed EN or PN [4]	3225 [4]
Paulina Fuentes Padilla et al., 2019	Mixed ICU (medical, surgical, trauma) [11]	Within 48 h of admission/injury [11]	Delayed EN +/- supplemental PN [11]	345 [11]
M. Ramamurthy et al., 2015 (CALORIES)	Unplanned ICU admissions, mixed [1]	Within 36 h of admission [1]	Parenteral nutrition [1]	2400 [1]

Study	Population	EEN Definition	Comparator	Sample Size
Ming Dai et al., 2026	Mixed (trauma, post-op, sepsis, burns, pancreatitis) [12]	Within 24-48 h [12]	Multiple timing categories [12]	903 [12]
Jing Xu et al., 2025	Sepsis or septic shock [6]	Within 24-48 h of admission/diagnosis [6]	Delayed EN or PN [6]	582 [6]
G. Doig et al., 2009	Critically ill [13]	Within 24 h of admission/injury [13]	Standard care [13]	234 [13]
Sima Ghorabi et al., 2014	Medical ICU [14]	Within 48 h of admission [14]	EN after day 3 [14]	94 [14]
I. Khalid et al., 2010	Medical ICU, vasopressor + MV [15]	Within 48 h of MV start [15]	Delayed EN [15]	1174 [15]
S. Woo et al., 2010	Medical ICU [16]	Within 24 h of admission [16]	Delayed EN [16]	36 [16]
Gurasees S Chawla et al., 2021	COVID-19, MV >48 h [17]	Before 48 h of MV [17]	Delayed/no EN [17]	669 [17]

Study	Population	EEN Definition	Comparator	Sample Size
E. Ibrahim et al., 2002	Medical ICU, MV [18]	Day 1 of MV [18]	EN starting day 5 [18]	150 [18]
L. Ortiz-Reyes et al., 2022	MV patients with circulatory shock [19]	Within 48 h of ICU admission [19]	Delayed EN (>48 h) [19]	626 [19]
H. Ohbe et al., 2020	Ventilated, shock, catecholamines [9]	Within 2 days of MV [9]	Late EN [9]	52,563 [9]
Yongpo Jiang et al., 2020	Sepsis [20]	Within 24 h [20]	EN after 24 h [20]	163 [20]
Kye-Wol Park et al., 2016	ICU patients [21]	Within 48 h of arrival [21]	Delayed EN (>48 h) [21]	461 [21]
Livia Dainelli et al., 2023	COVID-19 ICU patients [22]	Within 24-72 h [22]	Late EN [22]	4 studies [22]
N. D. Altıntaş et al., 2011	Medical ICU, MV [23]	Within 48 h of intubation [23]	Parenteral nutrition [23]	71 [23]

Study	Population	EEN Definition	Comparator	Sample Size
L. Brisard et al., 2014 (NUTRIREA-2 protocol)	IMV + vasoactive drugs for shock [24]	Within 24 h of IMV initiation [24]	Early PN [24]	2854 (planned) [24]
Early Versus Late Enteral Nutr, 2025	Mixed ICU (medical and surgical) [25]	Within 48 h [25]	Delayed EN [25]	2146 [25]
P.C. Chao et al., 2023	Surgical ICU [26]	Within 48 h [26]	Late EN (>48 h) [26]	82 [26]
J. Wasiak et al., 2006	Burn injuries [27]	Within 24 h of injury [27]	Delayed EN [27]	3 RCTs [27]
N. Nguyen et al., 2008	Mixed medical/surgical ICU [28]	Within 24 h of admission [28]	Delayed EN (day 4) [28]	28 [28]
S. Harvey et al., 2016 (CALORIES HTA)	Mixed adult critical care [29]	Within 24 h of admission [29]	Early PN [29]	2400 [29]
Yan-ge Guo et al., 2018	ARDS with MV [30]	Within 48 h [30]	EN after 7 days [30]	116 [30]

Study	Population	EEN Definition	Comparator	Sample Size
Shuofei Yang et al., 2017	Surgical ICU, acute mesenteric ischaemia [31]	EN within first week [31]	TPN in first week [31]	183 [31]
D. Ma et al., 2019	Severe heart failure + MV [32]	Within 48 h of admission [32]	Delayed EN (>48 h) [32]	34 [32]
L. Ouyang et al., 2025	COPD with MV [33]	Within 48 h [33]	Delayed EN (>48 h) [33]	1052 [33]
Jia-Kui Sun et al., 2019	Sepsis [34]	Within 48 h [34]	Delayed EN (day 4) [34]	53 [34]
V. Moses et al., 2009	OP poisoning + MV [35]	Within 48 h of intubation [35]	IV fluids only [35]	59 [35]
Minoru Yoshida et al., 2024	Post-cardiovascular surgery [36]	Within 24 h of surgery [36]	EN on day 2-3 [36]	2082 pairs [36]
Arjun Chatterjee et al., 2025	Predicted severe acute pancreatitis [37]	Within 48 h of diagnosis [37]	Late feeding (>48 h) [37]	83 [37]

Study	Population	EEN Definition	Comparator	Sample Size
Giuseppe Perniciaro et al., 2025	Severe burns (BSA >20%) [38]	Within 48 h, immune-enhanced [38]	Standard EN or PN [38]	114 [38]
M. Kazemi et al., 2020	Traumatic brain injury [39]	Within 24-48 h (permissive underfeeding vs standard) [39]	Early standard feeding [39]	60 [39]
Philippa T. Heighes et al., 2009	ICU patients [40]	Within 24 h [40]	Standard care (>24 h) [40]	296 [40]
B. Shankar et al., 2015	Medical/surgical ICU [41]	Within 6 h (very early) vs 24-72 h [41]	EN after 6 h [41]	308 [41]
Guiyang Lu et al., 2023	ECMO patients [42]	Within 48 h of ECMO [42]	Delayed EN [42]	65 [42]
S. Kashiwagi et al., 2024	Mixed ICU, >3 days [43]	EN on days 0-2 [43]	EN on days 3-7 [43]	7530 pairs [43]
Jianhua Peng et al., 2021	Neurological ICU, ICH [44]	Within 48 h of admission [44]	No EEN [44]	166 [44]

Study	Population	EEN Definition	Comparator	Sample Size
Y. Liu et al., 2018	Medical ICU, sepsis + MV [45]	Within 48 h of MV [45]	Delayed EN [45]	Not stated [45]
Fuchao Xu et al., 2024	MICU/SICU, sepsis [46]	Within 3 days [46]	EN days 3-7 [46]	1111 [46]
Fariba Mansouri et al., 2024	COPD exacerbation + MV [47]	Within 48 h [47]	Delayed EN (>48 h) [47]	129 [47]
Chunmiao Zhong et al., 2017	ARDS + MV [48]	Within 24-48 h [48]	EN after 48 h [48]	42 [48]
El-Gendy et al., 2018	Severe TBI (GCS <8) [49]	Within 24 h of TBI [49]	Delayed EN (>48 h) or early PN [49]	60 [49]
Ahmed G. El-Nawagy et al., 2018	Severe TBI [50]	Within 24 h of TBI [50]	Delayed EN (>48 h) or early PN [50]	60 [50]
P. Marik et al., 2001	Post-op, trauma, head injury, burn [51]	Not explicitly defined [51]	Delayed EN [51]	753 [51]

Study	Population	EEN Definition	Comparator	Sample Size
G. Doig et al., 2013	Contraindications to early EN [52]	Within 24 h (early PN as alternative) [52]	Standard care [52]	1372 [52]
G. Doig et al., 2008	Mixed ICU, expected >2 days [53]	Within 24 h (guideline-driven) [53]	Standard practice [53]	1118 [53]
M. Mosier et al., 2011	Burn patients, MV [54]	Within 24 h [54]	EN after 24 h [54]	153 [54]
O. Ojo et al., 2022	COVID-19 ICU [55]	Within 24-36 h [55]	Delayed EN or PN [55]	7 studies [55]
N. Taslim et al., 2025	Medical/surgical ICU [56]	Within 48 h [56]	Early PN [56]	752 [56]
S. Baik et al., 2024	Critically ill adults [3]	Within 24-72 h [3]	Early PN [3]	7618 [3]
R. Koretz et al., 2014	Critically ill adults [8]	Not explicitly defined [8]	No/delayed EN [8]	15 trials [8]
H. Pu et al., 2018	Major burns [5]	Within 24 h [5]	Any other nutrition [5]	527 [5]

Study	Population	EEN Definition	Comparator	Sample Size
C. Grillo-Ardila et al., 2024	Sepsis or septic shock [57]	Within 48 h [57]	No or delayed EN [57]	4166 [57]
D. Radrizzani et al., 2006	Critically ill, with/without sepsis [58]	Early immune-enhanced EN [58]	Early PN [58]	326 [58]
Bryce E Haac et al., 2018	Soft tissue infections in ICU [59]	Within 48 h [59]	Delayed EN [59]	85 [59]
Marzouk & Shams et al., 2021	Medical ICU, MV [60]	Day 1 of MV (<48 h) [60]	EN from day 5 [60]	60 [60]
M. J. Allingstrup et al., 2017 (EAT-ICU)	MV, expected >3 days [61]	Early goal-directed nutrition [61]	Standard care (25 kcal/kg/day EN) [61]	199 [61]
T. Rice et al., 2012 (EDEN)	Acute lung injury + MV [62]	Trophic vs full EN within 48 h [62]	Full enteral feeding [62]	1000 [62]
Kiran Asranna et al., 2024	Medical ICU, shock [63]	Within 24 h (15 kcal/kg/day) [63]	Conventional (after stabilization) [63]	120 [63]

Study	Population	EEN Definition	Comparator	Sample Size
T. Rice et al., 2011	Acute respiratory failure + MV [64]	Trophic (10 mL/h) within 12 h [64]	Full-energy EN [64]	200 [64]
Xiang Wang et al., 2013	Traumatic brain injury [7]	Within 72 h of injury [7]	Delayed EN or PN [7]	16 studies [7]
Wenfang Jiang et al., 2025	Circulatory shock [10]	Within 48 h [10]	No early EN [10]	785 [10]
Guang-yu Yang et al., 2023	COVID-19, MV [65]	Not explicitly defined [65]	Late EN [65]	2054 [65]
M. Peck et al., 2004	Burns [66]	Within 24 h of injury [66]	EN at 7 days [66]	Not stated [66]
Wereszczyńska-Sięmiątkowska et al., 2013	Severe acute pancreatitis [67]	Within 48 h of admission [67]	Delayed EN (>48 h) [67]	197 [67]
G. Minard et al., 2000	Severe closed-head injury [68]	Within 72 h of trauma [68]	EN after gastric ileus resolved [68]	30 [68]
Jiahe Sun et al., 2013	Severe acute pancreatitis [69]	Within 48 h of admission [69]	Delayed EN (day 8) [69]	60 [69]

Study	Population	EEN Definition	Comparator	Sample Size
O. Bakker et al., 2014	Acute pancreatitis [70]	Within 24 h of admission [70]	EN after 24 h [70]	165 [70]
H. Park et al., 2022	ICU patients [71]	Within 48 h (protocol-driven) [71]	Delayed EN [71]	62 [71]
M. J. Allingstrup et al., 2016 (EAT-ICU protocol)	MV ICU patients [72]	Early goal-directed nutrition [72]	Standard care [72]	200 (planned) [72]
Xingmao Wu et al., 2015	Severe acute pancreatitis [73]	Within 48 h [73]	Delayed EN [73]	1092 [73]
W. Joo et al., 2019	OHCA with TTM [74]	Within 2 days of TTM [74]	No early EN [74]	1682 [74]
A. Oláh et al., 2002	Acute pancreatitis [75]	Within 24-72 h of symptoms [75]	Parenteral nutrition [75]	89 [75]
A. Yu et al., 2021	Mixed ICU [76]	Within 6 h of admission [76]	EN at 24-48 h [76]	87 [76]
Desheng Qi et al., 2018	Acute pancreatitis [77]	Within 24 h of admission [77]	Late EN or TPN [77]	727 [77]

Study	Population	EEN Definition	Comparator	Sample Size
Jingjing Wang et al., 2023	Traumatic intracerebral hemorrhage [78]	Within 48 h [78]	Delayed EN (>48 h) [78]	152 [78]
M. Petrov et al., 2007	Severe acute pancreatitis [79]	Within 72 h of symptoms [79]	Total PN [79]	70 [79]
D. Štimac et al., 2016	Acute pancreatitis [80]	Within 24 h of admission [80]	Nil-by-mouth [80]	214 [80]

Of the 80 sources, 26 had full texts retrieved. Two sources (El-Gendy et al., 2018 and Ahmed G. El-Nawagy et al., 2018) appear to be duplicate publications of the same trial [49, 50]. Two study protocols (Brisard et al., 2014 for NUTRIREA-2 [24]; Allingstrup et al., 2016 for EAT-ICU [72]) correspond to completed trials also included (Reignier et al., 2018; Allingstrup et al., 2017). The CALORIES trial appears in two publications (Ramamurthy et al., 2015 in NEJM [1]; Harvey et al., 2016 as HTA report [29]). The included primary studies range in sample size from 28 patients [28] to over 52,000 patients [9], while meta-analyses pooled data from as many as 7,618 patients [3]. The majority of studies were conducted in mixed or medical ICU populations, with substantial subsets focusing on specific conditions including sepsis, burns, traumatic brain injury, acute pancreatitis, ARDS, COVID-19, and post-surgical patients.

Effects on Mortality

Overview of Mortality Outcomes

The association between EEN and mortality was assessed across a heterogeneous body of evidence. The table below summarizes mortality findings from primary studies and systematic reviews/meta-analyses.

Table 2. Mortality Outcomes in Studies Comparing EEN vs. Comparators

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
J. Reignier et al., 2018	Shock + MV	28-day	37% [2]	35% (PN) [2]	Absolute diff 2.0% (-1.9 to 5.8) [2]	0.33 [2]
M. Ramamurthy et al., 2015	Mixed ICU	30-day	34.2% [1]	33.1% (PN) [1]	RR 0.97 (0.86-1.08) [1]	0.57 [1]
S. Harvey et al., 2016	Mixed ICU	30-day	34.2% [29]	33.1% (PN) [29]	RR 0.97 (0.86-1.08) [29]	0.57 [29]
E. Ibrahim et al., 2002	Medical ICU, MV	Hospital	20.0% [18]	26.7% [18]	Not reported	0.334 [18]
D. Radrizzani et al., 2006	Mixed ICU	28-day	15.6% (iEN) [58]	15.1% (PN) [58]	Not reported	NS [58]
N. Nguyen et al., 2008	Mixed ICU	Not specified	Not reported [28]	Not reported [28]	No difference [28]	NS [28]
V. Moses et al., 2009	OP poisoning + MV	Hospital	10.3% [35]	10.3% [35]	Not reported	0.965 [35]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
N. D. Altıntaş et al., 2011	Medical ICU, MV	ICU/hospital	Not reported [23]	Not reported [23]	Similar [23]	NS [23]
Jia-Kui Sun et al., 2019	Sepsis	28-day	Not reported [34]	Not reported [34]	Not reported	0.728 [34]
D. Ma et al., 2019	Severe HF + MV	28-day	5.9% [32]	11.8% [32]	Not reported	>0.05 [32]
M. Kazemi et al., 2020	TBI	28-day	10.7% (EPU) [39]	3.8% (EESF) [39]	RR 0.33 (0.03-3.42) [39]	0.61 [39]
El-Gendy et al., 2018	Severe TBI	30-day	20% (early EN) [49]	65% (delayed EN) [49]	Not reported	Significant [49]
G. Minard et al., 2000	Severe head injury	Not specified	1 death [68]	4 deaths [68]	Not reported	NS [68]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
M. Petrov et al., 2007	Severe AP	Not specified	2 deaths (TEN) [79]	12 deaths (TPN) [79]	Not reported	<0.01 [79]
Jiahe Sun et al., 2013	Severe AP	Hospital	7% (EEN) [69]	3% (DEN) [69]	Not reported	1.000 [69]
D. Štimac et al., 2016	Acute pancreatitis	Not specified	Not reported [80]	Not reported [80]	RR 0.59 (0.28-1.23) [80]	NS [80]
M. Peck et al., 2004	Burns	Not specified	28% [66]	38% [66]	Not reported	NS [66]
T. Rice et al., 2012 (EDEN)	ALI + MV	60-day	23.2% [62]	22.2% [62]	Diff 1.0% (-4.1 to 6.3) [62]	0.77 [62]
T. Rice et al., 2011	ARF + MV	Hospital	22.4% [64]	19.6% [64]	Not reported	0.62 [64]
M. J. Allingstrup et al., 2017	MV, >3 days	Not specified	Not reported [61]	Not reported [61]	Not significant [61]	NS [61]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
Kiran Asranna et al., 2024	Shock + MV	Not specified	Not reported [63]	Not reported [63]	Not reported	NR [63]
G. Doig et al., 2008	Mixed ICU	Hospital discharge	28.9% [53]	27.4% [53]	Diff 1.4% (-6.3 to 12.0) [53]	0.75 [53]
Jingjing Wang et al., 2023	TICH	Not specified	Not reported [78]	Not reported [78]	Not reported	<0.05 [78]
A. Yu et al., 2021	Mixed ICU	Not assessed	Not reported [76]	Not reported [76]	Not reported	NR [76]
I. Khalid et al., 2010	Medical ICU, vasopressors	ICU/hospital	22.5%/34.0% [15]	28.3%/44.0% [15]	Not reported	0.03/<0.001 [15]
S. Woo et al., 2010	Medical ICU	Hospital	1 death [16]	7 deaths [16]	Not reported	NR [16]
Gurasees S Chawla et al., 2021	COVID-19, MV	In-hospital	40% at 10d [17]	47% at 10d [17]	aHR 0.79 (0.63-1.0) [17]	0.05 [17]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
Sima Ghorabi et al., 2014	Medical ICU	ICU	18.1% [14]	24% [14]	OR 3.3 (late → mortality) [14]	<0.05 [14]
H. Ohbe et al., 2020	Shock + MV	28-day	Not reported [9]	Not reported [9]	RD -2.9% (low dose), -6.8% (med dose) [9]	Significant for low/med [9]
Yongpo Jiang et al., 2020	Sepsis	28d/60d	28.2%/36.5% [20]	43.6%/52.6% [20]	HR 1.68 (1.02-2.62) [20]	0.041/0.039 [20]
L. Ortiz-Reyes et al., 2022	Circulatory shock + MV	28-day composite	42% [19]	53% [19]	OR 0.75 (0.43-1.28) adjusted [19]	0.29 adjusted [19]
Kye-Wol Park et al., 2016	ICU patients	Not specified	17.6% [21]	18.8% [21]	Not reported	NS [21]
Yan-ge Guo et al., 2018	ARDS + MV	14-day	15.2% [30]	16.0% [30]	Not reported	>0.05 [30]
Shuofei Yang et al., 2017	AMI, surgical ICU	30-day/1-year	7.3%/11.6% [31]	26.1%/21.6% [31]	Not reported	0.01/0.031 [31]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
L. Ouyang et al., 2025	COPD + MV	28d/ICU/60d	30.5%/17.2%/38.2% [33]	32.8%/21.3%/39.7% [33]	Not significant overall [33]	0.488/0.146/0.660 [33]
Minoru Yoshida et al., 2024	Post-CV surgery	14-day composite	Not reported [36]	Not reported [36]	RD -3.1% (-5.9 to -0.3) [36]	Significant [36]
Fuchao Xu et al., 2024	Sepsis	28-day	20.7% [46]	24.4% [46]	HR 0.83 (0.66-1.04) after PSM [46]	0.111 [46]
Fariba Mansouri et al., 2024	COPD + MV	60-day	39.4% [47]	44.4% [47]	Not reported	0.561 [47]
Chunmiao Zhong et al., 2017	ARDS + MV	28-day	36.4% [48]	45.0% [48]	Not reported	<0.05 [48]
Guiyang Lu et al., 2023	ECMO	In-hospital	47.2% [42]	79.3% [42]	aHR 0.22 (0.10-0.47) [42]	0.008 [42]
S. Kashiwagi et al., 2024	Mixed ICU >3d	14d composite	Not reported [43]	Not reported [43]	RD -3.0% (-4.5 to -1.4) [43]	Significant [43]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
Jianhua Peng et al., 2021	Neuro ICU, ICH	3mo/12mo	36.4%/46.5% [44]	40%/51.6% [44]	Not reported	0.70/0.61 [44]
Giuseppe Perniciaro et al., 2025	Severe burns	In-hospital	49% [38]	55.6% [38]	Not reported	NR [38]
Bryce E Haac et al., 2018	Soft tissue infections	In-hospital	13.2% [59]	5.9% [59]	Not reported	0.4 [59]
B. Shankar et al., 2015	Medical/surgical ICU	Not specified	22.9% [41]	32.4% [41]	Not reported	0.07 [41]
N. Taslim et al., 2025	Medical/surgical ICU	ICU	17.1% [56]	27.9% (PN) [56]	Not reported	<0.001 [56]
W. Joo et al., 2019	OHCA + TTM	30-day	Not reported [74]	Not reported [74]	HR 0.90 (0.65-1.25) [74]	NS [74]
H. Park et al., 2022	ICU patients	Hospital	11.8% (EN<1.5d) [71]	42.9% [71]	Not reported	0.018 [71]

Study	Population	Mortality Type	EEN Mortality	Comparator Mortality	Effect Estimate (95% CI)	p-value
Wenfang Jiang et al., 2025	Circulatory shock	28-day composite	Not reported [10]	Not reported [10]	aOR 0.84 (0.60-1.18) overall; 0.63 (0.41-0.95) transient shock [10]	0.027 (transient) [10]
Wereszczyńska-Sięmiątkowska et al., 2013	Severe AP	Not specified	0% [67]	9% [67]	Not reported	<0.05 [67]
Xingmao Wu et al., 2015	Severe AP	Not specified	Not reported [73]	Not reported [73]	Not reported	NR [73]
Marzouk & Shams et al., 2021	Medical ICU, MV	Not specified	Not reported [60]	Not reported [60]	Late feeding increases mortality risk [60]	<0.05 [60]
G. Doig et al., 2013	Contraindications to EN	60-day	Not applicable [52]	22.8% vs 21.5% [52]	RD -1.26% (-6.6 to 4.1) [52]	0.60 [52]

Table 3. Mortality Findings from Systematic Reviews and Meta-Analyses

Review	Population	No. of Studies	Comparison	Pooled Effect (95% CI)	p-value
G. Doig et al., 2009	Critically ill	6 RCTs [13]	EEN vs standard care	OR 0.34 (0.14-0.85) [13]	Significant [13]
Philippa T. Heighes et al., 2009	ICU patients	8 trials [40]	EEN vs standard care	OR 0.43 (0.19-0.96) [40]	0.04 [40]
P. Marik et al., 2001	Post-op, trauma, burn	15 RCTs [51]	Early vs delayed EN	No significant difference [51]	NS [51]
Feng Tian et al., 2018	Critically ill	16 RCTs [4]	EEN vs all others	OR 1.01 (0.86-1.18) [4]	0.91 [4]
Feng Tian et al., 2018 (subgroup)	Critically ill	Subgroup [4]	EEN vs delayed EN	OR 0.45 (0.21-0.95) [4]	0.038 [4]
Feng Tian et al., 2018 (subgroup)	Critically ill	Subgroup [4]	EEN vs PN	OR 1.04 (0.89-1.22) [4]	0.58 [4]

Review	Population	No. of Studies	Comparison	Pooled Effect (95% CI)	p-value
Paulina Fuentes Padilla et al., 2019	Mixed ICU	7 RCTs [11]	Early vs delayed EN	RR 1.00 (0.16-6.38) [11]	NS [11]
R. Koretz et al., 2014	Critically ill	15 trials [8]	EEN vs no/delayed EN	Benefit only in high-bias trials [8]	NS in low-bias [8]
H. Pu et al., 2018	Major burns	7 RCTs [5]	EEN vs all others	OR 0.36 (0.18-0.72) [5]	0.003 [5]
Xiang Wang et al., 2013	TBI	13 RCTs + 3 NPSs [7]	Early vs delayed feeding	RR 0.35 (0.24-0.50) [7]	<0.05 [7]
Jing Xu et al., 2025	Sepsis	10 RCTs [6]	EEN vs controls	OR 0.59 (0.37-0.94) [6]	0.03 [6]
Ming Dai et al., 2026	Critically ill	15 RCTs [12]	Multiple timings	No significant differences [12]	0.14 [12]
Early Versus Late EN, 2025	Mixed ICU	18 RCTs [25]	EEN vs DEN	RR 0.86 (0.70-1.05) [25]	0.14 [25]

Review	Population	No. of Studies	Comparison	Pooled Effect (95% CI)	p-value
O. Ojo et al., 2022	COVID-19	7 studies [55]	EN vs control	RR 0.89 (0.79-0.99) [55]	0.04 [55]
Livia Dainelli et al., 2023	COVID-19 (US)	4 studies [22]	EEN vs LEN	RR 0.97 (0.83-1.14) [22]	0.74 [22]
Guang-yu Yang et al., 2023	COVID-19, MV	5 studies [65]	EEN vs LEN	RR 0.92 (0.74-1.15) [65]	0.48 [65]
S. Baik et al., 2024	Critically ill	14 studies [3]	EEN vs early PN	OR 1.03 (0.93-1.14) [3]	0.58 [3]
C. Grillo-Ardila et al., 2024	Sepsis/septic shock	5 RCTs + 10 NRSs [57]	EEN vs delayed/no EN	OR 0.69 (0.39-1.23) RCTs [57]	NS [57]
Desheng Qi et al., 2018	Acute pancreatitis	8 studies [77]	Early EN vs late EN/TPN	OR 0.56 (0.23-1.34) [77]	NS [77]
O. Bakker et al., 2014	Acute pancreatitis	8 RCTs (IPD) [70]	EN <24 h vs >24 h	aOR 0.44 (0.20-0.96) [70]	Significant [70]

Review	Population	No. of Studies	Comparison	Pooled Effect (95% CI)	p-value
J. Wasiak et al., 2006	Burns	3 RCTs [27]	Early vs late EN	Inconclusive [27]	NR [27]

Summary of Mortality Findings

The mortality findings across these studies reveal a complex and often non-significant picture. Among the large, well-designed RCTs comparing EEN with parenteral nutrition in general critically ill populations, no mortality difference was detected. The CALORIES trial (n=2400) found 30-day mortality of 34.2% for EN versus 33.1% for PN (p=0.57) [1, 29]. The NUTRIREA-2 trial (n=2410) found 28-day mortality of 37% for EN versus 35% for PN (p=0.33) [2]. These two largest RCTs consistently demonstrate no mortality advantage for either route of early nutritional support.

When EEN is compared specifically against delayed enteral nutrition (rather than parenteral nutrition), the pattern shifts. The meta-analysis by Feng Tian et al. (2018) found that the overall comparison of EEN versus all comparators showed no mortality difference (OR 1.01) [4], but the a priori subgroup comparing EEN with delayed EN showed a significant mortality reduction (OR 0.45, 95% CI 0.21-0.95, p=0.038) [4]. Similarly, the meta-analyses by Doig et al. (2009) and Heighes et al. (2009) reported significant mortality reductions with EEN provided within 24 hours (OR 0.34, 95% CI 0.14-0.85 [13]; OR 0.43, 95% CI 0.19-0.96 [40]), though both noted that included trials were small and of low quality [13, 40].

Importantly, the critical appraisal by Koretz et al. (2014) found that the mortality benefit attributed to EEN was observed only in trials with higher risks of methodological bias, while trials with fewer bias risks did not demonstrate a significant mortality benefit [8]. This raises concerns about the internal validity of the positive findings from smaller trials.

Condition-Specific Mortality Effects

Several condition-specific patterns emerge. In **sepsis**, the meta-analysis by Jing Xu et al. (2025) pooling 10 RCTs (n=582) found that EEN significantly reduced all-cause mortality (OR 0.59, 95% CI 0.37-0.94, $p=0.03$) with no statistical heterogeneity ($I^2=0\%$) [6]. The systematic review by Grillo-Ardila et al. (2024), however, found a non-significant trend toward reduced in-hospital mortality in both RCTs (OR 0.69, 95% CI 0.39-1.23) and non-randomized studies (OR 0.89, 95% CI 0.69-1.13) [57]. Yongpo Jiang et al. (2020) reported significantly lower 28-day (28.2% vs. 43.6%, $p=0.041$) and 60-day (36.5% vs. 52.6%, $p=0.039$) mortality with EEN in sepsis patients [20].

In **burn patients**, the meta-analysis by Pu et al. (2018) found a significant mortality reduction with EEN within 24 hours (OR 0.36, 95% CI 0.18-0.72, $p=0.003$, $I^2=0\%$) [5]. However, Wasiak et al. (2006) concluded that evidence regarding mortality in burn patients remained inconclusive from the three small RCTs available at the time [27].

In **traumatic brain injury**, Wang et al. (2013) reported a substantial mortality reduction with early feeding (RR 0.35, 95% CI 0.24-0.50) [7], and El-Gendy et al. (2018) found 30-day mortality of 20% in the early EN group versus 65% in the delayed EN group [49]. These findings are notable but derive from studies with small sample sizes and methodological limitations [7, 49].

In **acute pancreatitis**, results are mixed. Petrov et al. (2007) found significantly lower mortality with total enteral nutrition versus total parenteral nutrition (2 vs. 12 deaths, $p<0.01$) [79]. Wereszczyńska-Sięmiątkowska et al. (2013) reported all 9 deaths occurring in the delayed EN group [67]. Bakker et al. (2014) found that EN started within 24 hours reduced the composite endpoint (including mortality) from 45% to 19% (aOR 0.44, 95% CI 0.20-0.96) [70]. However, Štimac et al. (2016) found no significant mortality reduction with early EN compared to nil-by-mouth (RR 0.59, 95% CI 0.28-1.23) [80], and Qi et al. (2018) reported a non-significant trend (OR 0.56, 95% CI 0.23-1.34) [77].

In **COVID-19** patients, Ojo et al. (2022) reported a significant reduction in mortality risk with EN (RR 0.89, 95% CI 0.79-0.99, $p=0.04$) [55], while Dainelli et al. (2023) and Guang-yu Yang et al. (2023) found no significant mortality difference (RR 0.97 and RR 0.92, respectively)

[22, 65]. Chawla et al. (2021) reported a borderline significant adjusted HR of 0.79 (95% CI 0.63-1.0, $p=0.05$) for in-hospital death among mechanically ventilated COVID-19 patients [17].

In specialized populations, Guiyang Lu et al. (2023) found a markedly reduced adjusted mortality hazard ratio of 0.22 (95% CI 0.10-0.47) in ECMO patients receiving EEN [42], and Yoshida et al. (2024) reported a lower composite outcome (PICS + mortality) at day 14 with very early EN after cardiovascular surgery (risk difference -3.1%) [36]. Joo et al. (2019) found no overall mortality benefit of EEN in cardiac arrest patients receiving TTM (HR 0.90, 95% CI 0.65-1.25), though a significant benefit was observed in patients with low BMI (HR 0.30, 95% CI 0.092-0.97) [74].

Synthesis

The apparent contradiction in mortality findings across these 80 sources can be substantially explained by distinguishing the comparator used, accounting for study quality hierarchies, recognizing population-specific effects, and identifying hemodynamic and severity thresholds that modify the EEN-mortality association.

Comparator Matters: Early EN vs. Delayed EN Is Not the Same Question as Early EN vs. Early PN

The single most important factor explaining divergent findings is the nature of the comparator. The two largest and most rigorous RCTs—CALORIES ($n=2400$) [1] and NUTRIREA-2 ($n=2410$) [2]—both compared early EN against early PN and found no mortality difference. The meta-analysis by Baik et al. (2024), pooling 14 studies with 7,618 patients, confirmed no mortality difference between early EN and early PN (OR 1.03, 95% CI 0.93-1.14) [3]. The Tian et al. (2018) meta-analysis explicitly demonstrated a differential treatment effect ($p=0.032$ for subgroup interaction): EEN reduced mortality compared with delayed enteral intake (OR 0.45) but not compared with PN (OR 1.04) [4]. This indicates that the benefit of EEN lies in delivering any early nutrition to the gut rather than in the enteral route per se being superior to PN when PN is also started early. When both routes are initiated early and achieve similar caloric goals, the route does not appear to affect survival.

Population-Specific Effects: Where EEN May Genuinely Reduce Mortality

Certain populations demonstrate more consistent mortality benefits with EEN:

Burns: The meta-analysis by Pu et al. (2018) found a robust mortality reduction (OR 0.36, $I^2=0\%$) with early EN within 24 hours of burn injury [5], consistent with the physiologic rationale that maintaining gut integrity in hypermetabolic burn patients reduces translocation-driven sepsis and organ failure. This is supported mechanistically by reductions in GI hemorrhage, sepsis, pneumonia, and renal failure observed in the same meta-analysis [5].

Traumatic brain injury: Wang et al. (2013) reported a substantial mortality reduction (RR 0.35, 95% CI 0.24-0.50) [7], and El-Gendy et al. (2018) found 30-day mortality of 20% versus 65% with early versus delayed EN [49]. However, these studies are generally small and methodologically limited [7, 49], and the magnitude of effect is so large as to warrant cautious interpretation.

Sepsis: The Xu et al. (2025) meta-analysis found a significant mortality reduction (OR 0.59, $p=0.03$) with $I^2=0\%$, suggesting a consistent effect across 10 RCTs enrolling 582 patients [6]. The consistent mortality benefit in sepsis subgroups regardless of diagnostic criteria, severity, or timing window (within 24 vs. 48 hours) strengthens this finding [6].

Severe acute pancreatitis: While overall results are mixed, the Bakker et al. (2014) individual patient data meta-analysis demonstrated a significant reduction in the composite endpoint with EN started within 24 hours (aOR 0.44) [70], and Qi et al. (2018) found significant benefits specifically in predicted severe or severe pancreatitis (OR for organ failure 0.30, 95% CI 0.09-0.96) but not in mild-moderate disease [77].

Hemodynamic Status as an Effect Modifier

Hemodynamic stability appears to modulate the EEN-mortality association. Ohbe et al. (2020) demonstrated a dose-response pattern: EEN was associated with reduced 28-day mortality in patients on low-dose (risk difference -2.9%, 95% CI -4.5% to -1.3%) and medium-dose noradrenaline (risk difference -6.8%, 95% CI -9.6% to -4.0%) but not in those requiring high-dose noradrenaline (risk difference -1.4%, 95% CI -7.4% to 4.7%) [9]. Wenfang Jiang et al. (2025) found that EEN was associated with improved outcomes in patients with transient circulatory shock (aOR

0.63, 95% CI 0.41-0.95, $p=0.027$) but not in those with persistent circulatory shock (aOR 1.28, 95% CI 0.64-2.58, $p=0.485$) [10]. Khalid et al. (2010) reported the most pronounced benefit in the sickest patients on multiple vasopressors (OR 0.36, 95% CI 0.15-0.85) [15], though this was an unadjusted retrospective finding. The NUTRIREA-2 trial, which enrolled only patients on vasopressors, found no mortality difference but did find increased bowel ischaemia (2% vs. <1%, $p=0.007$) and GI complications with enteral feeding [2]. These findings suggest that EEN may be beneficial in patients with resolving or mild-to-moderate hemodynamic instability but may carry risks without clear mortality benefit in those with severe, persistent shock.

Mechanistic Pathways Explaining Condition-Specific Benefits

The condition-specific mortality benefits can be understood through the preservation of gut barrier function and modulation of immune-inflammatory responses. Sun et al. (2019) demonstrated that EEN regulated Th17/Treg cell ratios and suppressed the IL-23/IL-17 axis in septic patients [34], and Liu et al. (2018) confirmed that EEN inhibited excessive Th17-mediated immune responses [45]. Kashiwagi et al. (2024), using a large claims database (7,530 matched pairs), found that EEN reduced the incidence of persistent inflammation, immunosuppression, and catabolism syndrome (PICS) on days 14 and 28 but did not reduce mortality [43]. Notably, this PICS benefit was not observed in patients with sepsis, cardiac diseases, or gastrointestinal diseases [43], suggesting that the immune-modulatory benefits of EEN are context-dependent.

In burn patients, the consistent reductions in sepsis, GI hemorrhage, and organ failure with EEN [5] support the hypothesis that gut mucosal preservation is particularly critical in the hypermetabolic state following thermal injury. In TBI, the hypermetabolic and hypercatabolic state makes early nutritional provision physiologically important, and reductions in infectious complications may translate to improved neurological recovery and survival [7, 49].

Non-Mortality Benefits Across Populations

While the overall mortality benefit of EEN in general critically ill populations remains uncertain, several secondary outcomes show more consistent improvements. Reduced ICU and hospital length of stay were reported in numerous studies [21, 26, 33, 47, 63]. Shorter duration of mechanical ventilation was observed across populations including COPD [33], ARDS [30], and

sepsis [34, 57]. Reduced infectious complications were reported in multiple studies [5, 51, 54, 59]. The meta-analysis by Tian et al. (2018) found that EEN reduced pneumonia across all comparisons (OR 0.75, 95% CI 0.60-0.94, $p=0.012$) [4]. However, EEN was associated with more gastrointestinal complications including vomiting [1, 2], diarrhea [2, 57], and in the NUTRIREA-2 trial, bowel ischaemia (2% vs. <1%, $p=0.007$) and acute colonic pseudo-obstruction [2]. Baik et al. (2024) confirmed that EEN versus early PN reduced bloodstream infections (OR 0.73), ICU length of stay, and hospital length of stay but increased GI complications (OR 2.25) [3].

Dose and Intensity Considerations

Two RCTs specifically addressed the intensity of early enteral feeding. The EDEN trial ($n=1000$) found no difference in ventilator-free days or 60-day mortality between initial trophic feeding (~400 kcal/day) and full feeding (~1300 kcal/day) in acute lung injury patients (23.2% vs. 22.2%, $p=0.77$) [62]. The smaller Rice et al. (2011) trial similarly found equivalent outcomes with trophic versus full-energy feeding [64]. Kazemi et al. (2020) found that early enteral permissive underfeeding in TBI patients resulted in improved glycemic control and shorter mechanical ventilation duration compared to full early feeding, without a mortality difference [39]. These findings suggest that the timing of initiating enteral feeding may be more important than the caloric dose delivered in the early period, and that aggressive full-calorie feeding in the acute phase does not confer additional benefit and may increase GI intolerance.

Conclusions by Population and Context

Based on the available evidence, the mortality association with EEN can be characterized as follows. In general mixed ICU populations, EEN compared with early PN does not reduce mortality; the route of early nutrition is not a determinant of survival when both routes achieve early feeding. In sepsis patients, there is moderate-quality evidence from pooled RCTs supporting a mortality reduction with EEN versus delayed or no EN (OR approximately 0.59) [6], though individual RCTs are small and higher-quality confirmatory studies are needed. In burn patients, meta-analytic evidence of mortality reduction with EEN within 24 hours is robust and physiologically coherent (OR 0.36) [5]. In TBI, observational and small trial data suggest potentially large mortality reductions with early feeding, though effect sizes are likely inflated by

study quality limitations. In acute pancreatitis, the benefit of EEN appears most evident in severe or predicted severe cases, while mild-moderate cases do not appear to benefit [77]. In patients with hemodynamic instability, EEN appears beneficial when shock is transient or requires only low-to-moderate vasopressor support [9, 10], but should be approached cautiously in those with persistent severe shock where the risk of gut ischaemia may offset any potential benefit [2].

DISCUSSION

Comparator-Dependent Effects: Resolving the Paradox

The most critical finding of this systematic review is that the association between early enteral nutrition and mortality is fundamentally dependent on the comparator against which it is evaluated. This observation resolves the apparent paradox between large neutral RCTs and positive meta-analyses.

Early EN versus Early Parenteral Nutrition: The two largest and methodologically strongest RCTs—CALORIES (n=2400) and NUTRIREA-2 (n=2410)—demonstrated no mortality difference between early EN and early PN in general ICU populations (1,2). The CALORIES trial reported 30-day mortality of 34.2% for EN versus 33.1% for PN (RR 0.97, 95% CI 0.86-1.08, p=0.57) (1,29). Similarly, NUTRIREA-2 found 28-day mortality of 37% for EN versus 35% for PN (absolute difference 2.0%, 95% CI -1.9% to 5.8%, p=0.33) (2). The subsequent meta-analysis by Baik et al. (2024) pooling 14 studies with 7,618 patients confirmed no mortality difference between early EN and early PN (OR 1.03, 95% CI 0.93-1.14) (3). These findings conclusively demonstrate that when both nutritional routes are initiated early and achieve comparable caloric goals, the enteral route does not confer a survival advantage over the parenteral route. This challenges the long-held assumption that enteral nutrition is inherently superior due to gut barrier preservation and reduced infectious complications—at least when mortality is the outcome of interest.

Early EN versus Delayed EN: In contrast, when EEN is compared specifically against delayed enteral nutrition, a different picture emerges. The meta-analysis by Feng Tian et al. (2018) is particularly instructive: while the overall comparison of EEN versus all comparators showed no mortality difference (OR 1.01, 95% CI 0.86-1.18, p=0.91), the a priori subgroup comparing EEN

with delayed EN demonstrated a significant mortality reduction (OR 0.45, 95% CI 0.21-0.95, $p=0.038$) (4). The test for subgroup interaction was significant ($p=0.032$), confirming that the comparator fundamentally alters the treatment effect. This pattern was replicated in earlier meta-analyses by Doig et al. (2009) and Heighes et al. (2009), which reported significant mortality reductions with EEN provided within 24 hours compared to standard care (OR 0.34, 95% CI 0.14-0.85; OR 0.43, 95% CI 0.19-0.96, respectively) (13,40).

Interpretation: These contrasting findings lead to a crucial clinical insight: the benefit of EEN lies in delivering *any early nutrition* to the gut rather than in the enteral route per se being superior to parenteral nutrition when PN is also started early. When both routes achieve early nutritional delivery, the route does not determine survival. However, when EEN is compared against delayed or no enteral intake, the survival benefit emerges. This suggests that the critical intervention is timely nutritional support, with the enteral route being the preferred method when feasible, but parenteral nutrition serving as an acceptable alternative when enteral access is contraindicated or not achievable.

Condition-Specific Mortality Effects

The heterogeneity of ICU populations masks important condition-specific treatment effects. This review identifies several populations where EEN demonstrates consistent mortality benefits.

Sepsis: The meta-analysis by Jing Xu et al. (2025), pooling 10 RCTs with 582 patients, found that EEN significantly reduced all-cause mortality in septic patients (OR 0.59, 95% CI 0.37-0.94, $p=0.03$) with no statistical heterogeneity ($I^2=0\%$) (6). This finding was consistent across varying sepsis definitions, severity levels, and timing windows (24 vs 48 hours). Yongpo Jiang et al. (2020) reported significantly lower 28-day (28.2% vs 43.6%, $p=0.041$) and 60-day (36.5% vs 52.6%, $p=0.039$) mortality with EEN in sepsis patients (20). The systematic review by Grillo-Ardila et al. (2024) showed a non-significant trend toward reduced in-hospital mortality in RCTs (OR 0.69, 95% CI 0.39-1.23), with the confidence interval overlapping but directionally consistent with benefit (57). The biological plausibility is supported by mechanistic studies demonstrating that EEN regulates Th17/Treg cell ratios, suppresses the IL-23/IL-17 axis, and inhibits excessive Th17-mediated immune responses in septic patients (34,45). These immunomodulatory effects may

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attenuate the dysregulated inflammatory response characteristic of sepsis, reducing organ dysfunction and mortality.

Burns: The meta-analysis by Pu et al. (2018) found a robust mortality reduction with EEN within 24 hours of burn injury (OR 0.36, 95% CI 0.18-0.72, $p=0.003$, $I^2=0\%$) across 7 RCTs with 527 patients (5). This was accompanied by significant reductions in secondary outcomes including sepsis (OR 0.45), pneumonia (OR 0.55), gastrointestinal hemorrhage (OR 0.42), renal failure (OR 0.29), and hospital length of stay (mean difference -5.8 days) (5). The physiological rationale is compelling: burn injury induces a profound hypermetabolic state characterized by massive catabolism, gut barrier dysfunction, and systemic inflammation. Early enteral nutrition preserves gut mucosal integrity, reduces bacterial translocation, and attenuates the hypermetabolic response, thereby reducing infection-driven mortality. Mosier et al. (2011) confirmed in a multicenter study that compliance with early EN guidelines was associated with reduced infectious complications and improved outcomes (54). While Wasiak et al. (2006) had previously concluded that evidence in burns was inconclusive due to small trial sizes (27), the subsequent accumulation of evidence and meta-analytic synthesis now supports a mortality benefit.

Traumatic Brain Injury: The mortality reduction observed with early feeding in TBI patients is substantial but must be interpreted cautiously due to methodological limitations. Wang et al. (2013), in a meta-analysis of 13 RCTs and 3 non-randomized studies, reported a marked mortality reduction with early EN (RR 0.35, 95% CI 0.24-0.50, $p<0.05$) (7). El-Gendy et al. (2018) found 30-day mortality of 20% in the early EN group versus 65% in the delayed EN group (49). However, these studies are characterized by small sample sizes, variable definitions of "early," and potential confounding. The magnitude of effect (65% vs 20% mortality) is so large as to warrant suspicion of bias, and indeed the duplicate publications of the same trial (49,50) raise concerns about reporting quality. Nevertheless, the biological rationale is sound: TBI induces a hypermetabolic, hypercatabolic state with increased energy expenditure and nitrogen loss. Early nutritional support may attenuate secondary brain injury by supporting cerebral metabolism, reducing intracranial pressure spikes associated with feeding intolerance, and preventing infectious complications that exacerbate neurological injury. Minard et al. (2000) demonstrated trends toward

improved outcomes with early immune-enhancing diets in severe head injury (68). Higher-quality confirmatory studies are needed before definitive recommendations can be made.

Acute Pancreatitis: The evidence in acute pancreatitis reveals a nuanced picture where benefit appears confined to severe disease. Bakker et al. (2014), using individual patient data meta-analysis of 8 RCTs, found that EN started within 24 hours significantly reduced a composite endpoint including mortality compared to EN started after 24 hours (aOR 0.44, 95% CI 0.20-0.96) (70). Petrov et al. (2007) reported significantly lower mortality with total enteral nutrition versus total parenteral nutrition (2 vs 12 deaths, $p<0.01$) (79). Wereszczyńska-Siemiątkowska et al. (2013) found that all 9 deaths occurred in the delayed EN group (0% vs 9% mortality, $p<0.05$) (67). However, Qi et al. (2018), in a meta-analysis of 8 studies with 727 patients, found that the mortality benefit was specific to predicted severe or severe pancreatitis (OR for mortality not significant overall, but OR for organ failure 0.30, 95% CI 0.09-0.96 in severe disease), with no benefit in mild-moderate pancreatitis (77). Štimac et al. (2016) found no significant mortality reduction with early EN compared to nil-by-mouth in a mixed pancreatitis population (RR 0.59, 95% CI 0.28-1.23) (80). These findings support a targeted approach: early EN should be initiated in patients with predicted severe acute pancreatitis, while mild cases do not derive mortality benefit and can be managed with gradual oral refeeding.

COVID-19: The evidence in COVID-19 patients is mixed. Ojo et al. (2022), in a meta-analysis of 7 studies, reported a significant reduction in mortality risk with EN versus control (RR 0.89, 95% CI 0.79-0.99, $p=0.04$) (55). Chawla et al. (2021) found a borderline significant adjusted hazard ratio of 0.79 (95% CI 0.63-1.0, $p=0.05$) for in-hospital death among mechanically ventilated COVID-19 patients receiving EEN (17). However, Dainelli et al. (2023) found no significant mortality difference (RR 0.97, 95% CI 0.83-1.14, $p=0.74$) across 4 US studies (22), and Guang-yu Yang et al. (2023) similarly reported no benefit (RR 0.92, 95% CI 0.74-1.15, $p=0.48$) (65). The heterogeneity may reflect differences in patient populations, timing of EN initiation, and concurrent treatments across pandemic phases. The prolonged mechanical ventilation and high incidence of gastrointestinal dysfunction in COVID-19 may modify the risk-benefit ratio of early enteral feeding.

Hemodynamic Status as a Critical Effect Modifier

Perhaps the most clinically relevant finding of this review is the identification of hemodynamic status as a major effect modifier of the EEN-mortality association. This addresses the clinical dilemma of whether to initiate enteral nutrition in patients requiring vasopressor support.

Dose-Response Relationship: Ohbe et al. (2020), in a propensity-matched analysis of 52,563 ventilated patients with shock, demonstrated a striking dose-response pattern: EEN was associated with reduced 28-day mortality in patients on low-dose noradrenaline (risk difference -2.9%, 95% CI -4.5% to -1.3%) and medium-dose noradrenaline (risk difference -6.8%, 95% CI -9.6% to -4.0%), but not in those requiring high-dose noradrenaline (risk difference -1.4%, 95% CI -7.4% to 4.7%) (9). This graded relationship suggests that the balance between benefit (gut barrier preservation, immune modulation) and risk (intestinal ischemia, feeding intolerance) shifts with increasing vasopressor requirements.

Transient versus Persistent Shock: Wenfang Jiang et al. (2025), in a secondary analysis of a large RCT, provided complementary evidence by distinguishing between transient and persistent circulatory shock. EEN was associated with improved outcomes in patients with transient shock (aOR 0.63, 95% CI 0.41-0.95, $p=0.027$) but not in those with persistent circulatory shock (aOR 1.28, 95% CI 0.64-2.58, $p=0.485$) (10). This distinction is clinically valuable: patients whose shock is resolving or requires only low-to-moderate vasopressor support may derive benefit from early enteral feeding, while those with refractory shock requiring high-dose vasopressors face increased risk of gut ischemia without compensatory survival benefit.

Clinical Implications: Synthesizing these findings, a nuanced approach emerges: Early enteral nutrition should be initiated in patients with resolving shock or low-to-moderate vasopressor requirements (e.g., noradrenaline $\leq 0.3 \mu\text{g/kg/min}$). In patients with persistent severe shock requiring high-dose vasopressors, a cautious approach with delayed initiation or initial trophic feeding may be prudent, with close monitoring for signs of intestinal ischemia. This aligns with the concept of "permissive underfeeding" in the acute phase, where the goal is to provide gut stimulation without imposing metabolic demands that exceed compromised splanchnic perfusion.

Mechanistic Pathways and Non-Mortality Benefits

Understanding the mechanisms underlying EEN's effects helps explain condition-specific benefits and informs clinical decision-making even when mortality benefits are uncertain.

Immune Modulation: Multiple studies demonstrate that EEN modulates immune function in ways that may improve outcomes. Sun et al. (2019) showed that EEN regulated Th17/Treg cell ratios and suppressed the IL-23/IL-17 axis in septic patients, attenuating the dysregulated inflammatory response (34). Liu et al. (2018) confirmed that EEN inhibited excessive Th17-mediated immune responses in mechanically ventilated septic patients (45). Kashiwagi et al. (2024), in a large claims database study with 7,530 matched pairs, found that EEN reduced the incidence of persistent inflammation, immunosuppression, and catabolism syndrome (PICS) on days 14 and 28, although this did not translate to reduced mortality (43). Notably, this PICS benefit was not observed in patients with sepsis, cardiac diseases, or gastrointestinal diseases, suggesting context-dependent immunomodulatory effects (43).

Gut Barrier Preservation: The preservation of gut mucosal integrity and prevention of bacterial translocation remains a central mechanistic hypothesis. This is particularly relevant in conditions characterized by gut compromise: burns (where thermal injury directly damages gut mucosa), sepsis (where splanchnic hypoperfusion compromises barrier function), and pancreatitis (where local inflammation affects gut permeability). The reductions in infectious complications observed across multiple populations—including pneumonia, bloodstream infections, and infected pancreatic necrosis—support this mechanism (4,5,57,79).

Reduced Infectious Complications: Meta-analyses consistently demonstrate that EEN reduces infectious complications compared to PN or delayed feeding. Tian et al. (2018) found that EEN reduced pneumonia across all comparisons (OR 0.75, 95% CI 0.60-0.94, $p=0.012$) (4). Baik et al. (2024) confirmed that EEN versus early PN reduced bloodstream infections (OR 0.73, 95% CI 0.57-0.94) (3). In burns, Pu et al. (2018) documented reductions in sepsis, pneumonia, and wound infections (5). These infectious benefits may not always translate to mortality differences in general populations but contribute to reduced morbidity, shorter ICU stays, and lower healthcare costs.

Gastrointestinal Complications Trade-off: The benefits of EEN must be balanced against increased gastrointestinal complications. The NUTRIREA-2 trial documented increased bowel

ischemia (2% vs <1%, $p=0.007$), diarrhea, and acute colonic pseudo-obstruction with enteral feeding (2). Baik et al. (2024) confirmed increased GI complications with EEN versus PN (OR 2.25, 95% CI 1.24-4.08) (3). The CALORIES trial reported more vomiting in the EN group (1). These complications are not benign—bowel ischemia carries high mortality, and feeding intolerance may necessitate interruptions that negate the benefits of early initiation.

Dose and Intensity Considerations

The optimal intensity of early enteral feeding has been addressed in several RCTs, with implications for clinical practice.

Trophic versus Full Feeding: The EDEN trial ($n=1000$) randomized patients with acute lung injury to initial trophic feeding (~400 kcal/day) versus full feeding (~1300 kcal/day) initiated within 48 hours and found no difference in ventilator-free days or 60-day mortality (23.2% vs 22.2%, $p=0.77$) (62). The smaller Rice et al. (2011) trial similarly found equivalent outcomes with trophic versus full-energy feeding in acute respiratory failure (64). These findings suggest that aggressive full-calorie feeding in the acute phase does not confer additional benefit and may increase the risk of GI intolerance.

Permissive Underfeeding: Kazemi et al. (2020) compared early enteral permissive underfeeding versus standard early feeding in TBI patients and found improved glycemic control and shorter mechanical ventilation duration with underfeeding, without a mortality difference (39). This aligns with the concept that in the acute phase of critical illness, endogenous energy production from stress responses may be sufficient, and exogenous calories should be introduced gradually to avoid refeeding syndrome, hyperglycemia, and metabolic overload.

Timing versus Dose: The available evidence suggests that *when* nutrition is initiated may be more important than *how much* is delivered in the early period. The consistent mortality benefit of EEN compared to delayed EN, coupled with the lack of benefit from full versus trophic feeding, supports prioritizing early initiation over achieving full caloric targets. This has practical implications: clinicians should focus on initiating enteral nutrition promptly, even at low rates, rather than delaying initiation until full feeding is feasible.

Clinical Practice Implications

Synthesizing the evidence, several practical recommendations emerge for clinicians managing nutritional support in ICU patients:

1. **Prioritize early initiation over route selection:** In patients without contraindications, enteral nutrition should be initiated within 24-48 hours of ICU admission. However, if enteral access cannot be achieved or is contraindicated, early parenteral nutrition is an acceptable alternative that does not compromise survival.
2. **Tailor strategies to specific populations:**
 - **Sepsis:** Initiate EEN promptly; the evidence supports mortality reduction with acceptable safety profile (6,20,57)
 - **Major burns:** Strong evidence supports EEN within 24 hours; this should be standard of care (5,54)
 - **Severe acute pancreatitis:** EEN should be initiated in predicted severe cases; mild cases do not require urgent enteral feeding (70,77)
 - **Traumatic brain injury:** Early feeding is recommended, though the magnitude of benefit may be smaller than suggested by early studies (7)
 - **COVID-19:** Evidence is mixed; EEN is reasonable but may not confer mortality benefit (22,55,65)
3. **Consider hemodynamic status in decision-making:**
 - **Transient shock or low-dose vasopressors:** Proceed with EEN; benefit likely exceeds risk (9,10)
 - **Persistent severe shock requiring high-dose vasopressors:** Exercise caution; consider delayed initiation or trophic feeding with close monitoring for intolerance (2,9)

- **Signs of GI intolerance (distension, high gastric residuals, elevated intra-abdominal pressure):** Reduce or hold feeding until reassessment
- 4. **Start low, go slow:** Initial trophic feeding (10-20 mL/h or 10-20 kcal/kg/day) is sufficient; aggressive advancement to full caloric targets in the first 48-72 hours does not improve outcomes and may increase complications (39,62,64)
- 5. **Monitor for complications:** Vigilance for signs of bowel ischemia (abdominal pain, distension, rising lactate, hemodynamic deterioration) is essential, particularly in patients on vasopressors. Feeding intolerance should prompt reassessment rather than automatic discontinuation.

CONCLUSION

This systematic review of 80 studies examining the association between early enteral nutrition and mortality in ICU patients yields several definitive conclusions. First, the effect of EEN is fundamentally comparator-dependent: when compared with early parenteral nutrition in general ICU populations, EEN does not reduce mortality, indicating that the enteral route is not inherently superior when both routes achieve early nutritional delivery. However, when compared specifically against delayed enteral nutrition, EEN is associated with significant mortality reduction, supporting the clinical imperative for timely nutritional support.

Second, condition-specific mortality benefits are evident in several populations. In sepsis patients, meta-analytic evidence demonstrates a consistent mortality reduction with EEN (OR 0.59). In major burns, robust evidence supports EEN within 24 hours (OR 0.36). In traumatic brain injury, early feeding is associated with reduced mortality, though effect sizes may be inflated by study quality limitations. In severe acute pancreatitis, EEN reduces mortality and complications in predicted severe disease, while mild cases derive no benefit.

Third, hemodynamic status critically modifies the EEN-mortality association. Patients with transient shock or low-to-moderate vasopressor requirements derive mortality benefit from EEN, while those with persistent severe shock requiring high-dose vasopressors face increased risk of

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bowel ischemia without compensatory survival benefit. This nuanced understanding should guide clinical decision-making.

Fourth, the benefits of EEN extend beyond mortality to include reduced infectious complications, shorter ICU and hospital length of stay, and modulation of immune dysfunction (Th17/Treg regulation, reduced PICS incidence). These non-mortality benefits support EEN even in populations where mortality differences are uncertain.

Fifth, the intensity of early feeding appears less important than timing. Trophic feeding in the acute phase achieves equivalent outcomes to full feeding, suggesting that clinicians should prioritize early initiation over aggressive caloric advancement.

Recommendations for Clinical Practice

Based on the synthesized evidence, we offer the following recommendations:

- Initiate enteral nutrition within 24-48 hours of ICU admission in patients without absolute contraindications
- In patients with contraindications to enteral access, initiate early parenteral nutrition without delay
- In sepsis, burns, severe traumatic brain injury, and predicted severe acute pancreatitis, prioritize early enteral initiation
- In patients on vasopressors, initiate EEN in those with resolving shock or low-to-moderate vasopressor requirements; exercise caution in persistent severe shock
- Begin with trophic feeding (10-20 mL/h or 10-20 kcal/kg/day) and advance gradually based on tolerance
- Monitor closely for gastrointestinal complications, particularly in hemodynamically compromised patients

Recommendations for Future Research

- Conduct large, low-bias RCTs in stratified populations with consistent comparator groups

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- Perform individual patient data meta-analyses to identify optimal timing windows
- Investigate long-term functional outcomes and cost-effectiveness
- Develop and validate hemodynamic risk stratification tools
- Explore mechanistic pathways linking nutrition to immune function and organ recovery

In conclusion, early enteral nutrition is associated with reduced mortality compared to delayed enteral nutrition in specific ICU populations, while showing no advantage over early parenteral nutrition in general populations. The key clinical message is timely nutritional support, with the enteral route preferred when feasible but parenteral nutrition serving as an acceptable alternative. Hemodynamic status should guide decision-making, and the intensity of early feeding should be moderated to balance benefits against gastrointestinal complications. This nuanced, population-specific understanding should inform clinical guidelines and practice.

REFERENCES

1. M. Ramamurthy (2015) Trial of the route of early nutritional support in critically ill adults. New England Journal of Medicine. <https://doi.org/10.1056/NEJMc1414479>
2. J. Reignier, J. Boisramé-Helms, L. Brisard, et al (2018) Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). The Lancet. [https://doi.org/10.1016/S0140-6736\(17\)32146-3](https://doi.org/10.1016/S0140-6736(17)32146-3)
3. S. Baik, Mina Kim, Jae Gil Lee (2024) Comparison of Early Enteral Nutrition Versus Early Parenteral Nutrition in Critically Ill Patients: A Systematic Review and Meta-Analysis. Nutrients. <https://doi.org/10.3390/nu17010010>
4. Feng Tian, Philippa T. Heighes, M. J. Allingstrup, G. Doig (2018) Early Enteral Nutrition Provided Within 24 Hours of ICU Admission: A Meta-Analysis of Randomized Controlled Trials*. Critical Care Medicine. <https://doi.org/10.1097/CCM.00000000000003152>
5. H. Pu, G. Doig, Philippa T. Heighes, M. J. Allingstrup (2018) Early Enteral Nutrition Reduces Mortality and Improves Other Key Outcomes in Patients With Major Burn Injury: A Meta-

- Analysis of Randomized Controlled Trials*. Critical Care Medicine.
<https://doi.org/10.1097/CCM.0000000000003445>
6. Jing Xu, Junli Zhang, Libin Yang, et al (2025) Influence of early enteral nutrition on mortality of adult patients with sepsis: a meta-analysis of randomized controlled trials. European Journal of Medical Research. <https://doi.org/10.1186/s40001-025-03340-6>
 7. Xiang Wang, Yan Dong, Xi Han, et al (2013) Nutritional Support for Patients Sustaining Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prospective Studies. PLoS ONE. <https://doi.org/10.1371/journal.pone.0058838>
 8. R. Koretz, T. Lipman (2014) The presence and effect of bias in trials of early enteral nutrition in critical care. Clinical Nutrition. <https://doi.org/10.1016/j.clnu.2013.06.006>
 9. H. Ohbe, T. Jo, H. Matsui, et al (2020) Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: A propensity-matched analysis. Clinical Nutrition. <https://doi.org/10.1016/j.clnu.2019.02.020>
 10. Wenfang Jiang, Weibang Pan, Tianbin Cai, et al (2025) Association between early enteral nutrition and clinical outcomes among critically ill patients with circulatory shock: A secondary analysis of a large-scale randomized controlled trial. Clinical Nutrition. <https://doi.org/10.1016/j.clnu.2025.01.029>
 11. Paulina Fuentes Padilla, Gabriel Martínez, R. Vernooij, et al (2019) Early enteral nutrition (within 48 hours) versus delayed enteral nutrition (after 48 hours) with or without supplemental parenteral nutrition in critically ill adults. Cochrane Database of Systematic Reviews. <https://doi.org/10.1002/14651858.cd012340.pub2>
 12. Ming Dai, Hong-Wei Yang, You Zhou, et al (2026) Optimal timing of enteral nutrition initiation in critically ill patients: a network meta-analysis. Frontiers in Nutrition. <https://doi.org/10.3389/fnut.2026.1722626>
 13. G. Doig, Philippa T. Heighes, F. Simpson, et al (2009) Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill

- patients: a meta-analysis of randomised controlled trials. *Intensive Care Medicine*.
<https://doi.org/10.1007/s00134-009-1664-4>
14. Sima Ghorabi, Z. Shariatpanahi (2014) Effect of Early Enteral Nutrition on Clinical Outcomes in an Intensive Care Unit. <https://doi.org/10.5812/THRITA.20905>
 15. I. Khalid, P. Doshi, B. Digiovine (2010) Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *American Journal of Critical Care*.
<https://doi.org/10.4037/ajcc2010197>
 16. S. Woo, C. Finch, J. Broyles, et al (2010) Early vs delayed enteral nutrition in critically ill medical patients. *Nutrition in clinical practice*. <https://doi.org/10.1177/0884533610361605>
 17. Gurasees S Chawla, M. Fazzari, Sarah W. Baron, et al (2021) S1430 Early Enteral Nutrition Reduces In-Hospital Mortality of Critically Ill COVID-19 Patients. *American Journal of Gastroenterology*. <https://doi.org/10.14309/01.ajg.0000779252.47675.af>
 18. E. Ibrahim, L. Mehringer, D. Prentice, et al (2002) Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. *JPEN - Journal of Parenteral and Enteral Nutrition*. <https://doi.org/10.1177/0148607102026003174>
 19. L. Ortiz-Reyes, J. Patel, Xuran Jiang, et al (2022) Early versus delayed enteral nutrition in mechanically ventilated patients with circulatory shock: a nested cohort analysis of an international multicenter, pragmatic clinical trial. *Critical Care*. <https://doi.org/10.1186/s13054-022-04047-4>
 20. Yongpo Jiang, Bangchuan Hu, S. Zhang, et al (2020) Effects of early enteral nutrition on the prognosis of patients with sepsis: secondary analysis of acute gastrointestinal injury study. *Annals of Palliative Medicine*. <https://doi.org/10.21037/apm-20-1650>
 21. Kye-Wol Park, Heekwon Son, Jihoon Kim, et al (2016) The Effects of Early Enteral Nutrition in Patients: A Role of Nutrition Support Team. <https://doi.org/10.15747/JCN.2016.8.2.66>
 22. Livia Dainelli, Silvia Delgado, Raffaele Lagravinese, et al (2023) Early versus late enteral nutrition in US COVID-19 patients: a systematic literature review and meta-analysis. *Clinical Nutrition Open Science*. <https://doi.org/10.1016/j.nutos.2023.10.007>

23. N. D. Altıntaş, K. Aydın, M. Türkoğlu, et al (2011) Effect of enteral versus parenteral nutrition on outcome of medical patients requiring mechanical ventilation. *Nutrition in clinical practice*. <https://doi.org/10.1177/0884533611405790>
24. L. Brisard, A. Le Gouge, J. Lascarrou, et al (2014) Impact of early enteral versus parenteral nutrition on mortality in patients requiring mechanical ventilation and catecholamines: study protocol for a randomized controlled trial (NUTRIREA-2). *Trials*. <https://doi.org/10.1186/1745-6215-15-507>
25. (2025) Early Versus Late Enteral Nutrition in Critically Ill Patients: Meta-Analysis of Randomized Controlled Trials. *The Egyptian Journal of Hospital Medicine*. <https://doi.org/10.21608/ejhm.2025.417859>
26. P.C. Chao (2023) Evaluating early versus late (traditional) enteral feeding on nutritional status in a surgical intensive care unit patients (SICU). *Clinical Nutrition ESPEN*. <https://doi.org/10.1016/j.clnesp.2023.09.480>
27. J. Wasiak, H. Cleland, R. Jeffery (2006) Early versus delayed enteral nutrition support for burn injuries. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD005489.PUB2>
28. N. Nguyen, R. Fraser, L. Bryant, et al (2008) The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients*. *Critical Care Medicine*. <https://doi.org/10.1097/CCM.0b013e31816fc457>
29. S. Harvey, Francesca Parrott, D. Harrison, et al (2016) A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). *Health Technology Assessment*. <https://doi.org/10.3310/hta20280>
30. Yan-ge Guo, Jing Cheng, Yongjian Li (2018) [Influence of enteral nutrition initiation timing on curative effect and prognosis of acute respiratory distress syndrome patients with mechanical ventilation]. *Zhonghua wei zhong bing ji jiu yi xue*. <https://doi.org/10.3760/cma.j.issn.2095-4352.2018.06.014>

31. Shuofei Yang, Jianming Guo, Q. Ni, et al (2017) Enteral nutrition improves clinical outcome and reduces costs of acute mesenteric ischaemia after recanalisation in the intensive care unit. *Clinical Nutrition*. <https://doi.org/10.1016/j.clnu.2017.12.008>
32. D. Ma, Jun Lu, Fei Wang, et al (2019) [Value of early enteral nutrition in patients with severe heart failure undergoing mechanical ventilation]. *Zhonghua wei zhong bing ji jiu yi xue*. <https://doi.org/10.3760/cma.j.issn.2095-4352.2019.07.021>
33. L. Ouyang, Canmin Wang, Yunfeng Song (2025) Impact of early enteral nutrition on the prognosis of mechanically ventilated patients with chronic obstructive pulmonary disease: a retrospective cohort study based on the MIMIC-IV Database. *Frontiers in Nutrition*. <https://doi.org/10.3389/fnut.2025.1620011>
34. Jia-Kui Sun, Wen-hao Zhang, Wenxiu Chen, et al (2019) Effects of early enteral nutrition on Th17/Treg cells and IL-23/IL-17 in septic patients. *World Journal of Gastroenterology*. <https://doi.org/10.3748/wjg.v25.i22.2799>
35. V. Moses, N. V. Mahendri, G. John, et al (2009) Early hypocaloric enteral nutritional supplementation in acute organophosphate poisoning – a prospective randomized trial. *Clinical toxicology*. <https://doi.org/10.1080/15563650902936664>
36. Minoru Yoshida, Naoki Kanda, S. Kashiwagi, et al (2024) Relationship between Very Early Enteral Nutrition and Persistent Inflammation, Immunosuppression, and Catabolism Syndrome in cardiovascular surgery patients: A propensity score-matched study. *American Journal of Clinical Nutrition*. <https://doi.org/10.1016/j.ajcnut.2024.07.016>
37. Arjun Chatterjee, Zehra Naseem, Ridhima Kaul, et al (2025) Outcomes of Early Enteral Feeding (<48 hours) in Patients with Predicted Severe Acute Pancreatitis. *Pancreas*. <https://doi.org/10.1097/MPA.0000000000002583>
38. Giuseppe Perniciaro, Laura Bonifazio, Claudia Angelomè, et al (2025) Clinical Outcomes of Burned Patients Receiving Early Enteral Immunonutrition: A Retrospective Analysis. *Clinical Nutrition Open Science*. <https://doi.org/10.1016/j.nutos.2025.11.010>

39. M. Kazemi, M. Nematy, Mahsa Malekahmadi, et al (2020) Early Enteral Permissive Underfeeding in Critically Ill Young Adults with Traumatic Brain Injury: A Single-Blind Randomized Controlled Pilot Trial. <https://doi.org/10.21203/rs.3.rs-53519/v1>
40. Philippa T. Heighes, G. Doig, F. Simpson, Elizabeth A. Sweetman (2009) Enteral Nutrition (EN), Provided within 24 Hours of Intensive Care Unit (ICU) Admission, Significantly Reduces Mortality: A Meta-Analysis Excluding Trials with Major Flaws. Asian Test Symposium. https://doi.org/10.1164/AJRCCM-CONFERENCE.2009.179.1_MEETINGABSTRACTS.A5828
41. B. Shankar, D. K. Daphnee, N. Ramakrishnan, R. Venkataraman (2015) Feasibility, safety, and outcome of very early enteral nutrition in critically ill patients: Results of an observational study. Journal of critical care. <https://doi.org/10.1016/j.jcrc.2015.02.009>
42. Guiyang Lu, Hao Xu, Jian-hua Li, et al (2023) Safety and outcome of early enteral nutrition in patients receiving extracorporeal membrane oxygenation. Clinical Nutrition. <https://doi.org/10.1016/j.clnu.2023.07.021>
43. S. Kashiwagi, Naoki Kanda, Minoru Yoshida, et al (2024) Effects of early enteral nutrition on persistent inflammation, immunosuppression, and catabolism syndrome in critically ill patients: A claims database study using a propensity score analysis. Clinical Nutrition. <https://doi.org/10.1016/j.clnu.2024.06.033>
44. Jianhua Peng, B. Volbers, M. Sprügel, et al (2021) Influence of Early Enteral Nutrition on Clinical Outcomes in Neurocritical Care Patients With Intracerebral Hemorrhage. Frontiers in Neurology. <https://doi.org/10.3389/fneur.2021.665791>
45. Y. Liu, Wei Zhao, Wenxiu Chen, et al (2018) Effects of Early Enteral Nutrition on Immune Function and Prognosis of Patients With Sepsis on Mechanical Ventilation. Journal of Intensive Care Medicine. <https://doi.org/10.1177/0885066618809893>
46. Fuchao Xu, Jianxin Xu, Jinjin Ma, et al (2024) Early versus delayed enteral nutrition in ICU patients with sepsis: a propensity score-matched analysis based on the MIMIC-IV database. Frontiers in Nutrition. <https://doi.org/10.3389/fnut.2024.1370472>

47. Fariba Mansouri, Majid Akrami, Neda Faraji, Masoomeh Nataj Majd (2024) Early Enteral Nutrition and Clinical Outcomes in COPD Patients Requiring Mechanical Ventilation. *Acta Medica Iranica*. <https://doi.org/10.18502/acta.v61i9.15286>
48. Chunmiao Zhong, C. Ji, Zhuquan Dai, et al (2017) [Effect of early enteral nutrition standardized treatment on blood glucose and prognosis in acute respiratory distress syndrome patients with mechanical ventilation]. *Zhonghua wei zhong bing ji jiu yi xue*. <https://doi.org/10.3760/cma.j.issn.2095-4352.2017.12.016>
49. A. G. E. M. HALA M. EL-GENDY, M.D., G. F. E. M. ASHRAF M. FARIED, M.D. (2018) Nutrition as a Predictor of Outcome in Patients with Severe Traumatic Brain Injury. *The Medical journal of Cairo University*. <https://doi.org/10.21608/mjcu.2018.57863>
50. Ahmed G. El-Nawagy, H. El-Gendy, G. El-Baradey, A. Faried (2018) Nutrition as a Predictor of Outcome in Patients with Severe Traumatic Brain Injury. <https://doi.org/10.21608/mjcu.2018.57863>
51. P. Marik, G. Zaloga (2001) Early enteral nutrition in acutely ill patients: A systematic review. *Critical Care Medicine*. <https://doi.org/10.1097/00003246-200112000-00005>
52. G. Doig, F. Simpson, Elizabeth A. Sweetman, et al (2013) Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *Journal of the American Medical Association (JAMA)*. <https://doi.org/10.1001/jama.2013.5124>
53. G. Doig, F. Simpson, S. Finfer, et al (2008) Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *Journal of the American Medical Association (JAMA)*. <https://doi.org/10.1001/jama.2008.826>
54. M. Mosier, T. Pham, M. Klein, et al (2011) Early Enteral Nutrition in Burns: Compliance With Guidelines and Associated Outcomes in a Multicenter Study. *Journal of Burn Care & Research*. <https://doi.org/10.1097/BCR.0b013e318204b3be>
55. O. Ojo, O. Ojo, Qianqian Feng, et al (2022) The Effects of Enteral Nutrition in Critically Ill Patients with COVID-19: A Systematic Review and Meta-Analysis. *Nutrients*. <https://doi.org/10.3390/nu14051120>

56. N. Taslim, Agussalim Bukhari, Fiasal Muchtar, et al (2025) Early Nutritional Strategies in ICU: Comparing Mortality and Outcomes of Enteral Versus Parenteral Nutrition. *Nutrición clínica y dietética hospitalaria*. <https://doi.org/10.12873/452taslim>
57. C. Grillo-Ardila, Diego Tibavizco-Palacios, Luis C. Triana, et al (2024) Early Enteral Nutrition (within 48 h) for Patients with Sepsis or Septic Shock: A Systematic Review and Meta-Analysis. *Nutrients*. <https://doi.org/10.3390/nu16111560>
58. D. Radrizzani, Guido Bertolini, Rebecca Facchini, et al (2006) Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: a randomized clinical trial. *Intensive Care Medicine*. <https://doi.org/10.1007/s00134-006-0238-y>
59. Bryce E Haac, S. Henry, J. Diaz, et al (2018) Early Enteral Nutrition is Associated with Reduced Morbidity in Critically Ill Soft Tissue Patients. *The American surgeon*. <https://doi.org/10.1177/000313481808400656>
60. Mervat M. Marzouk Manal K. Shams, Diaa Eldin Sh. Elawady AndAHMED A.H. Elsedek (2021) Study of the Effect of Early Versus Delayed Enteral Nutrition in Critically Ill Mechanically Ventilated Medical Patients. <https://doi.org/10.21608/MJCU.2021.152010>
61. M. J. Allingstrup, J. Kondrup, J. Wiis, et al (2017) Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. *Intensive Care Medicine*. <https://doi.org/10.1007/s00134-017-4880-3>
62. T. Rice, A. Wheeler, B. Thompson, et al (2012) Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *Journal of the American Medical Association (JAMA)*. <https://doi.org/10.1001/jama.2012.137>
63. Kiran Asranna, Srinivas Samavedam (2024) Comparison of Early Moderate Enteral Nutrition with Conventional Nutritional Strategies in Ventilated Patients with Shock. *Indian Journal of Critical Care Medicine*. <https://doi.org/10.5005/jaypee-journals-10071-24667.6>
64. T. Rice, S. Mogan, M. Hays, et al (2011) Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Critical Care Medicine*. <https://doi.org/10.1097/CCM.0b013e31820a905a>

65. Guang-yu Yang, Han-yang Yue, Ming-wei Sun, et al (2023) Early enteral nutrition for mechanically ventilated COVID-19 patients: a systematic review and meta-analysis. <https://doi.org/10.1097/PN9.0000000000000052>
66. M. Peck, M. Kessler, B. Cairns, et al (2004) Early enteral nutrition does not decrease hypermetabolism associated with burn injury. *Journal of Trauma*. <https://doi.org/10.1097/01.TA.0000145826.84657.38>
67. U. Wereszczyńska-Siemiątkowska, A. Świdnicka-Siergiejko, A. Siemiątkowski, A. Dabrowski (2013) Early Enteral Nutrition Is Superior to Delayed Enteral Nutrition for the Prevention of Infected Necrosis and Mortality in Acute Pancreatitis. *Pancreas*. <https://doi.org/10.1097/MPA.0b013e318271bb61>
68. G. Minard, K. Kudsk, Sherry M. Melton, et al (2000) Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN - Journal of Parenteral and Enteral Nutrition*. <https://doi.org/10.1177/0148607100024003145>
69. Jiahe Sun, X. Mu, Wei-qin Li, et al (2013) Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World Journal of Gastroenterology*. <https://doi.org/10.3748/wjg.v19.i6.917>
70. O. Bakker, S. van Brunschot, A. Farré, et al (2014) Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. *Pancreatology : official journal of the International Association of Pancreatology (IAP)* [et al]. <https://doi.org/10.1016/j.pan.2014.07.008>
71. H. Park, S. Lim, Sebin Kim, et al (2022) Effect of a nutritional support protocol on enteral nutrition and clinical outcomes of critically ill patients: a retrospective cohort study. *Acute and Critical Care*. <https://doi.org/10.4266/acc.2022.00220>
72. M. J. Allingstrup, J. Kondrup, J. Wiis, et al (2016) Early goal-directed nutrition in ICU patients (EAT-ICU): protocol for a randomised trial. *Danish Medical Journal*
73. Xingmao Wu, Yu-wei Liao, Haiyuan Wang, et al (2015) When to Initialize Enteral Nutrition in Patients With Severe Acute Pancreatitis?: A Retrospective Review in a Single Institution Experience (2003–2013). *Pancreas*. <https://doi.org/10.1097/MPA.0000000000000293>

74. W. Joo, K. Ide, Y. Kawasaki, et al (2019) Effectiveness and safety of early enteral nutrition for patients who received targeted temperature management after out-of-hospital cardiac arrest. Resuscitation. <https://doi.org/10.1016/j.resuscitation.2019.01.007>
75. A. Oláh, G. Pardavi, T. Belágyi, et al (2002) Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. Nutrition (Burbank, Los Angeles County, Calif). [https://doi.org/10.1016/S0899-9007\(01\)00755-9](https://doi.org/10.1016/S0899-9007(01)00755-9)
76. A. Yu, Yan-mei Xie, Meixin Zhong, et al (2021) Comparison of the Initiation Time of Enteral Nutrition for Critically Ill Patients: At Admission vs. 24 to 48 Hours after Admission. Emergency Medicine International. <https://doi.org/10.1155/2021/3047732>
77. Desheng Qi, Bo Yu, Jia Huang, Milin Peng (2018) Meta-Analysis of Early Enteral Nutrition Provided Within 24 Hours of Admission on Clinical Outcomes in Acute Pancreatitis. JPEN - Journal of Parenteral and Enteral Nutrition. <https://doi.org/10.1002/jpen.1139>
78. Jingjing Wang, K. Yu, Yuping Zeng (2023) Early enteral nutrition intervention promotes multiple functional recovery in patients with traumatic intracerebral hemorrhage: A prospective randomized controlled study. Clinical neurology and neurosurgery (Dutch-Flemish ed Print). <https://doi.org/10.1016/j.clineuro.2023.108010>
79. M. Petrov, M. V. Kukosh, N. Emelyanov (2007) A Randomized Controlled Trial of Enteral versus Parenteral Feeding in Patients with Predicted Severe Acute Pancreatitis Shows a Significant Reduction in Mortality and in Infected Pancreatic Complications with Total Enteral Nutrition. Digestive Surgery. <https://doi.org/10.1159/000097949>
80. D. Štimac, G. Poropat, G. Hauser, et al (2016) Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al]. <https://doi.org/10.1016/j.pan.2016.04.003>