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Timing of Enteral Nutrition in Intensive Care: A Machine-Learning-Assisted Automated Meta-Analysis Using Robust Bayesian Model Averaging

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 February 2026 and was last updated on 11 February 2026.

INTRODUCTION

Review question / Objective This systematic review and Bayesian meta-analysis aimed to evaluate the clinical impact of early versus delayed initiation of enteral nutrition (EN) among critically ill patients, integrating robust Bayesian model averaging (RoBMA), machine-learning-driven literature screening, and AI-assisted data extraction to provide transparent and precise evidence synthesis.

Condition being studied The condition under investigation is the metabolic and nutritional derangement commonly experienced by critically ill patients admitted to the Intensive Care Unit (ICU). This condition is characterized by a state of hypermetabolism, negative nitrogen balance, and impaired immune function. These physiological disturbances significantly contribute to increased patient morbidity and mortality, as well as prolonged length of stay in the ICU. Optimal nutritional management, specifically the timing for initiating enteral nutrition (EN), is a critical intervention aimed at addressing this condition. The clinical controversy and practice variation lie in defining the optimal window for starting EN support, often categorized as "early" versus "delayed" initiation, to improve clinical outcomes in this vulnerable patient population.

METHODS

Participant or population The participants addressed in this review are adult patients (≥18 years old) admitted to Intensive Care Units (ICUs). The included studies comprise diverse critically ill populations from various clinical contexts, including but not limited to trauma, surgical, medical, and COVID-19 ICU patients.

Intervention The intervention evaluated is the initiation of early enteral nutrition (EN). This is defined specifically as the start of EN support within 24 hours of ICU admission. The review assesses this strategy in comparison to delayed EN initiation strategies.

Comparator The comparator applied is the initiation of delayed enteral nutrition (EN). This refers to strategies where EN support is started later than the early intervention group, without a single strict time threshold applied across all included studies.

Study designs to be included The review will include randomized controlled trials (RCTs) and high-quality observational studies, specifically those employing propensity-score matching (PSM) or robust retrospective cohort designs.

Eligibility criteria Studies involving pediatric or other special populations.
Abstracts without available full texts.
Studies not clearly differentiating between early and delayed timing of EN initiation.

Information sources A comprehensive literature search was performed in five electronic databases: PubMed, Scopus, Embase, Web of Science, and the Cochrane Library, from their inception until June 30, 2025. Search results were imported into EndNote X20 for initial deduplication, followed by manual confirmation of duplicates using the revtools package in R.

Main outcome(s) Twenty-two comparisons from 21 eligible studies (14 randomized trials and 8 propensity-score-matched observational studies) comprising diverse ICU populations were included. Bayesian cumulative evidence analysis strongly supported the initiation of early EN (within 24 hours) over delayed strategies, significantly reducing mortality (BF10 = 472.99), infectious and gastrointestinal complications, and ICU LOS. Subgroup analyses revealed consistent benefits across various clinical contexts, with the most pronounced advantages observed in trauma and surgical ICU populations. High methodological heterogeneity persisted, mitigated partially by robust Bayesian modeling. AI-assisted screening and data extraction demonstrated high accuracy (≥94%) and inter-rater reliability (κ=0.91).

Quality assessment / Risk of bias analysis The methodological quality and risk of bias (RoB) of included studies were assessed using a hybrid AI-assisted pipeline. For randomized controlled trials, the revised Cochrane RoB2 tool was employed. For observational studies, the ROBINS-I tool was used.
The process involved pre-processing full-text study documents into structured text segments. These segments were then classified by a fine-tuned RoBERTa-based deep learning model, which assessed multiple domains of methodological quality (e.g., randomization, blinding, outcome reporting). Each RoB domain prediction from the classifier was associated with a confidence score.

High-confidence predictions (confidence ≥0.8) were accepted directly into the RoB assessment. Predictions below this threshold underwent manual review by trained human reviewers. The RoB model demonstrated an overall accuracy of 89.3%, an F1-score of 0.87, and an inter-rater agreement of κ = 0.84.

All RoB evaluations were summarized visually using domain-specific bar plots (RoB2) and radar plots (ROBINS-I).

Strategy of data synthesis A Bayesian model-averaged meta-analysis (RoBMA) was conducted using the R package "RoBMA". This approach systematically combined multiple statistical models through Bayesian model averaging to address publication bias, small-study effects, and model uncertainty. The combined models included fixed-effects, random-effects, selection, and precision-effect (PET-PEESE) models.

Primary outcomes (mortality, complications) were analyzed as binary endpoints using pooled odds ratios (ORs) with 95% credible intervals (CrI). Secondary outcomes (ICU length-of-stay) were analyzed as continuous variables using pooled mean differences (MDs) with 95% CrI.

The analyses utilized weakly informative priors to minimize subjective influence. Subgroup and meta-regression analyses were performed to explore heterogeneity sources based on predefined moderators (study design, patient population, timing definitions, publication year).

Sensitivity analyses were conducted to examine the robustness of results, including: adjusting the scale of prior distributions for effect sizes and heterogeneity; performing leave-one-out analyses by excluding individual studies; and applying different combinations of model specifications.

Publication bias was assessed using Egger's regression, Begg's rank correlation tests, funnel plot visualizations, and Bayesian model selection weighting within the RoBMA framework.

All statistical analyses were performed using Python 3.12.

Subgroup analysis Subgroup analyses were performed based on predefined moderators to explore sources of heterogeneity. The moderators included:

Study design (randomized controlled trials vs. observational studies)

Patient populations (e.g., trauma/surgical ICU, general ICU, COVID-19 patients)

Definitions of enteral nutrition timing (e.g., initiation within 24 hours ["very early"] versus ≤72 hours ["moderately early"])

The analyses were conducted for the three main outcomes: complications, ICU length of stay (LOS), and mortality. Results demonstrated a consistent reduction in risk or improvement in outcome across all subgroups for each outcome. Notably, trauma/surgical ICU patients showed greater relative benefits compared to other populations. Defining early EN as within 24 hours consistently resulted in a more pronounced beneficial effect compared to later definitions.

Sensitivity analysis Several sensitivity analyses were conducted to examine the robustness of the results:

Prior distribution sensitivity: The sensitivity of results to prior distribution choices was examined by adjusting the scale of the prior distributions for effect sizes (odds ratios and mean differences) and the heterogeneity parameter (τ^2). Weak priors (SD = 2), standard priors (SD = 1), and strong priors (SD = 0.5) were applied.

Leave-one-out analysis: Individual studies were sequentially excluded from the analysis, and the Bayesian model averaging (RoBMA) was repeated to assess the influence of each study on the overall effect estimate.

Model specification analysis: Different combinations of model specifications, including fixed-effect, random-effect, selection, and PET-PEESE precision-adjusted models, were applied to examine their impact on the pooled effect size, credible interval (CrI), and Bayes factor (BF10).

Heterogeneity diagnostics: Baujat plot analysis was performed to identify studies contributing significantly to overall results and heterogeneity. An exclusion analysis was also conducted to see if removing any individual study significantly altered the direction of the pooled effect estimates.

Country(ies) involved Beijing Pinggu Hospital, China.

Keywords Enteral nutrition;Intensive care; Bayesian meta-analysis; Machine learning; Artificial intelligence.

Contributions of each author

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