# INPLASY PROTOCOL

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**Corresponding author:**
**Peng li**

**lipbenzi@126.com**

**Author Affiliation:**
**Beijing hospital, national center of gerontology.**

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**Conflicts of interest:**
**None declared.**

# Effect of supplemental parenteral nutrition on mortality in critically ill adult patients: a meta-analysis and sub-group analysis

Li, P[1]; Liu, JJ[2].

**Review question / Objective:** **Several observational studies demonstrated that increased nutrition deliver by supplementary parenteral nutrition (SPN) plus enteral nutrition (EN) could reduce the rate of mortality in critically ill patients. Therefore, we aimed to compare and evaluate the effect of SPN plus EN for critically ill patients.**
**Eligibility criteria:** **Inclusion criteria: 1) Study types: published randomized controlled clinical studies or cohort studies; 2) Study subjects: adult patients with severe illness; 3) Intervention: The experimental group was given SPN combined with EN nutritional support treatment; 4) Control: the control group was given EN nutritional support or other nutritional support; 5) Outcome indicators: mortality, infection, length of hospital stay and ICU stay, mechanical ventilation duration.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 July 2022 and was last updated on 08 July 2022 (registration number INPLASY202270045).

## INTRODUCTION

**Review question / Objective:** **Several observational studies demonstrated that increased nutrition deliver by supplementary parenteral nutrition (SPN) plus enteral nutrition (EN) could reduce the rate of mortality in critically ill patients. Therefore, we aimed to compare and evaluate the effect of SPN plus EN for critically ill patients.**

**Rationale:** **Many studies have demonstrated that the supplementary parenteral nutrition (SPN) refers to a mixed nutritional support method, in which part of the energy and protein is supplemented by PN when EN is insufficient. Studies have**

found that reasonable SPNs can meet the energy and protein needs of critically ill patients, promote protein synthesis, adjust nitrogen balance, improve nutritional status, and even reduce complications and improve prognosis. SPN is at risk of overfeeding, with risks of hyperglycemia, liver dysfunction, prolonged mechanical ventilation, and infection. However, a recent retrospective cohort study enrolling 182 lung cancer patients showed that early intervention with SPN reduces the incidence of granulocytopenia-related infections (P<0.05). Moreover, in a meta-analysis combining five studies which compared clinical outcomes of SPN+EN versus EN alone for critically ill patients, Alsharif and his colleagues found that SPN+EN could significantly decrease the risk of ICU mortality (RR=0.569, P=0.030), especially for those with high malnutrition risk (mNUTRIC score ≥5 or BMI 0.05). At present, the results of early SPN-related research on mortality have not been determined, and different countries or societies have different opinions on SPN recommendations. This study aims to evaluate the impact of SPN treatment on the risk of mortality among critically ill patients.

**Condition being studied:** Studies were considered eligible if they met these criteria: Inclusion criteria: 1) Study types: published randomized controlled clinical studies or cohort studies; 2) Study subjects: adult patients with severe illness; 3) Intervention: The experimental group was given SPN combined with EN nutritional support treatment; 4) Control: the control group was given EN nutritional support or other nutritional support; 5) Outcome indicators: mortality, infection, length of hospital stay and ICU stay, mechanical ventilation duration. Exclusion criteria: 1) duplicate publications; 2) single-arm study; 3) pediatric patients; 4) case report, animal study, meeting report, review; 5) with incomplete outcome.

## METHODS

**Search strategy:** We searched Pubmed (source, PubMed from January 2005 to May 2019), EMBASE (January 2005 to May 2021), the Cochrane Library (to May 2021), Google Scholar (to May 2021), SinoMed database (to May 2021) and the ClinicalTrials.gov website (to May 2021) using the terms supplemental parenteral nutrition, parenteral nutrition, enteral nutrition, critically ill. No language restrictions were applied.

**Participant or population:** Adult patients with severe illness.

**Intervention:** The experimental group was given SPN combined with EN nutritional support treatment

**Comparator:** The control group was given EN nutritional support or other nutritional support.

**Study designs to be included:** Published randomized controlled clinical studies or cohort studies.

**Eligibility criteria:** Inclusion criteria: 1) Study types: published randomized controlled clinical studies or cohort studies; 2) Study subjects: adult patients with severe illness; 3) Intervention: The experimental group was given SPN combined with EN nutritional support treatment; 4) Control: the control group was given EN nutritional support or other nutritional support; 5) Outcome indicators: mortality, infection, length of hospital stay and ICU stay, mechanical ventilation duration.

**Information sources:** Pubmed, EMBASE, the Cochrane Library , Google Scholar, SinoMed database and the ClinicalTrials.gov website.

**Main outcome(s):** Primary outcome was all-cause mortaltiy.

**Additional outcome(s):** Secondary outcomes were rate of infection, mechanical ventilation duration, length of hospital stay and ICU stay.

**Data management:** All analyses were performed according to the intention-to-

treat principle. Statistical significance was set at 0.05 for the Z-test for OR. Results were analyzed quantitatively with STATA 12.0 (StataCorp LP, College Station, TX).

**Quality assessment / Risk of bias analysis:** The PRISMA (Preferred Reporting Items for Systemic Reviews and Meta- Analyses) statement was followed for quality evaluation [20]. Quality assessment was undertaken independently by two reviewers. We used the Newcastle-Ottawa scale (NOS) to evaluate the methodological quality [21]. NOS scale varies from 0 to 9 stars using eight criteria that cover three components: patient selection, study groups comparability, and outcomes assessment. Studies with a NOS score of 6 and more were considered as "high quality", while those with a score less than 6 as "low quality".

**Strategy of data synthesis:** Data analysis was completed by three reviewers. Pooled odds risk (OR) for dichotomous outcomes and standardized mean difference (SMD) for continuous outcomes was calculated with 95% confidence intervals (CI).

**Subgroup analysis:** Based on the mean level of baseline clinical data (study' design, patients' age, APACHE II score, SPN initiating time and follow-up duration), the study's type was divided into "RCT" and "cohort study"; age was classified into "<60.0 years" and "≥60.0 years"; APACHE II score was classified into "48h)"; follow-up duration was reported as "<30 d" and "≥30d".

**Sensitivity analysis:** Sensitivity analysis was done by eliminating each study at one time to evaluate the influence of each trial on the primary outcome and the robustness of the result.

**Language:** No language restriction.

**Country(ies) involved:** China, Beijing hospital, national center of gerontology.

**Other relevant information:** In the meta-analyses, trial sequential analysis (TSA) was used to reduce the risk of reaching a false-negative conclusion [26]. When the cumulative Z-curve crossed the trial sequential monitoring boundary or entered the futility area, a sufficient level of evidence for the anticipated intervention effect was reached, and no further trials were needed. If the Z-curve did not cross any of the boundaries and the required information size (RIS) had not been reached, evidence to reach a conclusion was insufficient, and more trials were needed to confirm the results. In this TSA for mortality, we estimated the RIS based on an RR reduction of 20%. The type I error (α) = 0.05 (two-sided) and power (1 – β) = 0.80. The control event proportions were 33% for mortality, which was calculated from the comparator group. The I2 values were 45.2%. The TSA was conducted using TSA Version 0.9.5.10 Beta (www.ctu.dk/tsa).

**Keywords:** supplemental parenteral nutrition; enteral nutrition; critically ill; mortality; meta-analysis.

**Contributions of each author:**

Author 1 - peng li - Author 1 drafted the manuscript.
Email: lipbenzi@126.com
Author 2 - Junjun liu - The author provided statistical expertise.
Email: since8895@126.com