Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Hospital de Clínicas de Porto Alegre

Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Tese de Doutorado

Infecção associada à Nutrição Parenteral: Estudo de Coorte Retrospectivo em Hospital Terciário e Revisão Sistemática e Meta-Análise sobre Associação de Nutrição Parenteral com Infecções e Mortalidade

Pedro Henrique Comerlato

Porto Alegre, 2021.

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Para Catalogação. A ser inserido após defesa da tese e correções.

Esta Tese de Doutorado será apresentada no formato sugerido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela é constituída de resumo da tese, uma breve introdução em português, dois artigos em inglês (o primeiro publicado no The Brazilian Journal of Infectious Diseases em 2020 e o segundo publicado no The American Journal of Clinical Nutrition em 2021), além de considerações finais em português.

Dedicatória

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Lista de Abreviaturas

CLABSI - Central Line–Associated Bloodstream Infection

CVC – Cateter Venoso Central / Central Venous Catheter

GRADE – Grading of Recommendations, Assessment, Development and Evaluations

ICU – Intensive Care Unit

LTC – Long-Term Catheter

NP – Nutrição Parenteral

NPT – Nutrição Parenteral Total

PICC – Peripherally Inserted Central Catheter

PN – Parenteral Nutrition

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses

RCT - Randomized Controlled Trials

TSA – Trial Sequential Analysis

Resumo

Nutrição parenteral (NP) é uma solução de nutrientes infundida por via endovenosa, visando oferecer calorias, aminoácidos, vitaminas, oligoelementos e eletrólitos para pacientes com indicação de suporte nutricional. Devido riscos inerentes aos procedimentos invasivos necessários, além da não utilização do trato gastrointestinal, esse tipo de suporte é reservado para pacientes com contraindicações ou intolerância à terapia nutricional enteral. Infecções são das complicações mais comuns, e se associam a maior morbimortalidade e custos hospitalares nesses pacientes. A presente tese buscou avaliar fatores de risco associados as complicações infecciosas e mortalidade em pacientes recebendo nutrição parenteral através de um estudo observacional realizado em um hospital terciário e uma revisão sistemática da literatura existente. Métodos: I) Estudo de coorte retrospectivo com revisão de prontuário de pacientes adultos hospitalizados submetidos à NP em hospital terciário no decorrer de dois anos e II) Revisão sistemática de estudos randomizados e observacionais que compararam desfechos quanto a hospitalização e óbito dos pacientes que receberam NP versus pacientes que não receberam tal intervenção, com meta-análise de estudos randomizados. Resultados e Conclusão: Identificou-se alta mortalidade nesse grupo de pacientes inerente à sua complexidade clínica, e não associada a NP isoladamente. Por outro lado, complicações infecciosas foram mais frequentes em pacientes nutridos de maneira parenteral, mesmo quando ajustados para possíveis fatores de confusão, com algumas particularidades que puderam ser exploradas graças ao tamanho da amostra - como sítio de infecção. Apesar da tradicional relação existente entre infecção de cateter venoso central e NP, essa não foi a principal complicação infeciosa desses pacientes. Na presente análise uma maior taxa de infecções sistêmicas, em especial infecções intra-abdominais, foi encontrada. De forma agregada, os resultados das duas análises auxiliam em aspectos práticos para manejo do paciente que necessita de NP. Além disso, sinaliza quais aspectos do conhecimento sobre essa área ainda merecem ser explorados.

Capítulo 1

Introdução

O estado nutricional de pacientes hospitalizados está associado a diversos desfechos clínicos e à mortalidade (1). Indivíduos que necessitam hospitalização, especialmente pacientes críticos, apresentam piora do estado nutricional devido à resposta inflamatória, ao estresse metabólico e à imobilidade (2). Suporte nutricional é uma alternativa para contornar esse problema, sendo indicada para pacientes incapazes de se nutrir ela via oral (3).

O aporte nutricional ao paciente hospitalizado pode ser ofertado por meio de nutrição enteral e/ou parenteral, na dependência da gravidade do quadro. A via enteral é preferida quando possível, pela vantagem de manter a integridade estrutural e funcional do trato gastrointestinal e por reduzir a resistência à ação da insulina (4). Já a via parenteral é escolhida ou associada frente a impossibilidade de atingir as necessidades nutricionais integral ou parcialmente pela via enteral (3).

A nutrição parenteral (NP) é uma solução de calorias, aminoácidos, eletrólitos, vitaminas, minerais, oligoelementos e fluidos infundida por via endovenosa (5). Pela característica hipertônica da solução, a administração dessa solução é preferencialmente fornecida por meio de acesso venoso central (6). Além das vantagens estruturais e metabólicas da nutrição enteral, os riscos inerentes ao procedimento invasivo necessário a NP também são considerados na hora da escolha da via nutricional (7).

Em adição aos riscos do procedimento invasivo da cateterização venosa, a NP é relacionada, ainda, a uma série de importantes efeitos adversos que incluem infecções (8), alterações metabólicas como hiperglicemia (9) e síndrome da realimentação (10).

Especificamente em relação a infecções, eventos localizados ou sistêmicos são frequentemente associados a pacientes que recebem tal suporte, podendo chegar a 18 eventos de infecção relacionada a cateter por 1000 cateteres-dia (11). Não é claro na literatura se essa elevada incidência é mediada

pelos dispositivos invasivos ou pela complexidade desses pacientes e presença de condições relacionadas, como desnutrição, hiperglicemia e disfunção multiorgânica (12, 13, 14). A associação, inclusive, não é unânime. Enquanto estudos mais antigos sugerem que a NP é um fator de risco independente para complicações infecciosas – como infecção pulmonar, abdominal e de corrente sanguínea associada ao cateter venoso (15,16), estudos mais recentes não encontraram a mesma relação (17, 18).

Uma hipótese para justificar essa discrepância é a de que essa taxa de infecção associada à NP esteja em redução, principalmente em função de melhorias nos cuidados de saúde, como: otimização da oferta calórica (evitando hipo ou hiperalimentação), melhora no controle glicêmico, na esterilidade dos componentes da dieta e nos cuidados quanto ao acesso venoso central (19).

A hiperalimentação era uma condição comum nos primórdios da terapia nutricional parenteral (20), bem como excesso de infusões de soluções glicosadas, que estão associadas a maior risco de hiperglicemia (21). A hiperglicemia sabidamente deprime a função imune e interfere na função fagocítica (22). Por outro lado, o tratamento intensivo com insulina (alvo de glicemia < 110mg/dL) também está associado com aumento de mortalidade por hipoglicemia (23). As evidências atuais sugerem que o alvo de glicose sanguínea seja abaixo de 180mg/dL, obtido tanto por meio de insulinoterapia quanto pela administração controlada de soluções glicosadas, com possível influência sobre taxas de complicações infecciosas (24).

A desnutrição também está relacionada com piores desfechos, pois, por meio da imunossupressão, associa-se com aumento do risco de infecções (25). Atualmente, protocolos orientam o melhor momento de iniciar dieta parenteral, evitando a subalimentação existente no passado e a postergação do suporte nutricional.

Nas últimas décadas, outro fator que vem contribuindo para melhora nas taxas de complicações infecciosas é o aumento da prescrição de soluções padronizadas, pela menor manipulação dos produtos e maior esterilidade farmacêutica dos materiais utilizados (26). Além disso, práticas de barreira máxima de proteção durante a inserção do cateter, protocolos de cuidados e

maior atenção para medidas de higiene antes da manipulação de dispositivos invasivos estão associadas a redução de infecções de corrente sanguíneas (27,28). Existem diversas questões abertas na literatura que podem interferir nas taxas de infecções nosocomiais nesses pacientes, tal como: sítio anatômico ideal para inserção do cateter venoso central, o tempo de utilização do cateter, características do dispositivo e a instalação exclusiva para o suporte nutricional.

Estudos observacionais com enfoque nas dúvidas clinicas relacionadas a NP e infecção de cateter ampliam o tamanho da população já estudada na literatura e podem auxiliar na identificação de variáveis associadas aos desfechos de interesse (29), desde que sejam realizados ajustes para os fatores de confusão até então mencionados (30). Já estudos de revisão sistemática e metanálises podem ser utilizados para compilar dados de estudos individuais e reunir de forma sumarizada as evidências disponíveis para fornecer respostas mais definitivas do que cada estudo individualmente (31). A abordagem sistematizada torna o processo de seleção de informações menos sujeito a vieses, ajuda a dirimir dúvidas em situações que os resultados dos estudos são conflitantes ou negativos e minimizando controvérsia (31).

Outro recurso que pode ser de auxílio é a técnica de Trial Sequential Analysis (TSA), ferramenta que avalia estatisticamente a confiabilidade dos resultados de metanálises (32), combinando técnicas de análises cumulativa, cálculo de tamanho amostral e ajustes para análises repetidas (32). Essa análise nos informa se há dados suficientes (poder total dos estudos incluídos) para definir se uma intervenção é benéfica, inócua ou associada a malefícios, estabelecida uma diferença mínima arbitrariamente (33).

As revisões existentes até o momento da conclusão dessa tese sobre o tema não realizaram ajustes para os fatores de confusão até então citados, e mais frequentemente incluem apenas pacientes críticos em suas análises (34). Além da divergência nas taxas de infecção, não é claro se tal risco, se existente, também confere maior taxa de mortalidade para essa população.

Considerando as divergências existentes na literatura e a necessidade de revisão sobre o tema (dados escassos em algumas populações específicas, ajuste para fatores de confusão como gravidade, hiperglicemia, fatores

específicos do cateter e da prescrição nutricional), essa tese teve como objetivo avaliar fatores de risco associados as complicações infecciosas e mortalidade em pacientes adultos hospitalizados recebendo nutrição parenteral através de um estudo observacional realizado em um hospital terciário e uma revisão sistemática da literatura existente.

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Capítulo 2

Artigo 1

Infectious complications associated with parenteral nutrition in intensive care unit and non-intensive care unit patients

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Abstract

Introduction: Malnutrition is associated with an increased risk of complications in hospitalized patients, and parenteral nutrition (PN) is used when oral or enteral feeding is not possible. This study aimed at analyzing associations between PN characteristics and infectious complications in hospitalized patients. **Material and methods:** This was a retrospective cohort study conducted in a tertiary-care university hospital. Data from consecutive adult patients submitted to PN (January 2016 to December 2017; ICU and ward) were reviewed by means of an electronic database. Patient's clinical characteristics, PN prescription and catheter insertion procedure data were extracted and analyzed. The main outcome was the development of central line–associated bloodstream infection (CLABSI). The secondary outcomes were other infectious complications and mortality, as well as factors associated with CLABSI. **Results:** We analyzed 165 patients and 247 catheters used for parenteral nutrition infusion. The CLABSI rate was 6.47 per 1000 catheter-days. In the univariable analysis, CLABSI was associated with longer hospitalization time, longer PN time, longer catheter time, catheter insertion performed by a surgeon or a surgical resident, and procedures performed outside the ICU. In an extended time-dependent Cox regression, no variable was associated with a higher risk of CLABSI, and additional PN days did not increase the rate of CLABSI. The overall mortality rate was 24.8%. Only the patients' comorbidity index was associated with death in the multivariable analysis. **Discussion:** In our study, patients who needed PN had an overall CLABSI rate of 6.47 per 1000 catheter-days. These outcomes were not associated with PN and catheter characteristics studied after adjustment for

catheter time. The overall mortality rate was 24.8% and it was not associated with PN in multivariable analyses, only with Charlson comorbidity index.

Introduction

Malnutrition is associated with an increased risk of complications, higher mortality rate, longer hospital stays, and higher hospitalization costs [1]. Nutritional support is an alternative to overcome this problem, and it is indicated for patients unable to feed orally [2]. There are two available options: enteral nutrition, usually chosen to preserve the patient's gastrointestinal transit [3], and parenteral nutrition (PN), used when it is impossible to achieve partial or full enteral nutrition requirements. A pragmatic multicenter randomized clinical trial evaluated PN versus enteral nutrition in ICU patients of developed countries and found no difference in both nutritional strategies in the mean number of treated infectious complications or 90-day mortality [4].

The infection rate related to a central venous catheter (CVC) used for PN varies according to the definition used. This rate can reach up to 18 infectious events per 1000 catheter-days, [5, 6], a larger number compared with central catheter infections in devices not used for PN (two infectious events per 1000 catheter-days in US intensive care units (ICUs) and 6.8 infectious events per 1000 catheter-days in developing countries' ICUs [7]). However, most central line infection data come from developed countries where resources differ (including the types of PN available and the device used for PN nutrition) from the emerging countries [8]. A multicentric Brazilian publication reported 10.22 bloodstream infections per 1,000 catheters/day, and the risk factors for infection were multiple−lumen catheters, duration of catheterization and length of stay in the ICU, but PN was not evaluated as a variable in this study [9]. Indeed, another study performed in the same country showed that PN was a risk factor for central venous catheter infection [10].

Most studies on infection rates of PN refer to specific populations, such as critically ill, cancer or trauma patients [5]. Few studies evaluated different diseases, non-critically-ill patients, catheter bundles and physicians experience insertion for CVC, using a recently inserted versus an already used catheter for nutrition purposes. Studying this more heterogeneous cohort may infer more associations with the route of nutrition itself and not regarding specific groups. Furthermore, characteristics of the vascular access correlated with increased odds of infection in PN users are unknown, and the recommendations regarding the best vascular access to PN present a low to very low quality of evidence [11]. Therefore, the aim of the present study is to examine mediators of PN and central line–associated bloodstream infection (CLABSI) association in a tertiary-care-level hospital. The secondary aim is to analyze the rate of other complications in patients submitted to PN.

Materials and Methods

We conducted a retrospective cohort study in an 800-bed tertiary-care university hospital in the south of Brazil through review of electronic medical records of all adult inpatients submitted to PN (January 2016 to December 2017). Patients who received PN for less than 72 hours were excluded from the analyses, as were those who received PN through a long-term catheter (LTC) due to their out-of-hospital use and possibility of lack of notification or even occurrence of an outcome in another institution. A peripherally inserted central catheter (PICC) were used in the hospital during the study only in experimental situations and they were not analyzed because of the possibility of bias due to differentiated care related to a new technology / device in the population. The study was approved by the local research ethics committee.

The assistant physician (based on local protocol and current guidelines) defined the choice for the total or supplementary PN [2, 3]. All of the prescribed solutions were two-in-one (2:1), combining glucose and amino acids, separately from intravenous lipid emulsion. The available solutions and the products used were Fresenius Kabi—Germany, Aminoven 10%, Lipovenos MCT 20%, and glucose 50%, with electrolytes, vitamin K, trace elements, and addition of multivitamins. Glycemic control during hospitalization was an attribution of the attending physician, as was the CVC installation, although they are both standardized procedures. The local protocol about care with central lines includes qualified personnel and a bundle for best care of CVC [12]. According to our hospital protocol, all physicians were encouraged to start enteral or oral diet and discontinue the PN solution as soon as possible and the device should be removed, since it is no longer necessary.

Demographics characteristics, clinical data [13-15], and aspects of CVC insertion were reviewed. Daily records from the insertion of the first CVC used for PN until discharge or death were revised. Patients were classified according to the indication for PN: total PN, when there was contraindication or intolerance to any amount of enteral or oral diet or supplemental PN, when it was not possibly to achieve the nutritional goal only with an enteral or oral diet. For each patient, the total hospitalization time, total PN time, total time with CVC in use, and the time between the CVC insertion and the start of PN were calculated.

The main outcome was the development of central line–associated bloodstream infection (CLABSI), defined as patients with CVC with clinical signs of infections and no other source of bacteremia, except the catheter up to 48

hours after the CVC's withdrawal, plus 1) one positive blood culture for a known pathogen or 2) two positive blood cultures for skin pathogen [16].

We also recorded as secondary outcomes other infections (pulmonary infection, abdominal infection, bacteremia not related to CVC, fungemia, urinary infection, operative wound infection based on clinical diagnosis), death, and hyperglycemia, as well as factors associated with CLABSI. Hyperglycemia was arbitrarily defined as at least four episodes of capillary glucose > 200 mg/dl during PN infusion; a need for a regular insulin prescription to achieve glycemic control; or a description of decompensated diabetes.

Sample size calculation was performed considering the 18.3% cumulative incidence of CLABSI in a study performed in a similar population in the same hospital [10]. It was estimated in 231 catheters evaluation to identify factors associated with CVC infection, considering a power of 95% and a margin of error of 5%.

Statistic analysis was conducted as appropriated. Continuous variables were reported as mean and standard deviation, median and interquartile range, or number of patients and percentages. The differences between the groups were analyzed with Student's *t*-test, Mann-Whitney *U*-test, or χ^2, as appropriate. Generalized estimating equations were used for comparison in relation to CVC (more than one device per patient is possible). In multivariable analysis independent variables were included in the model according to their significance in the univariate analysis ($p < 0.05$) or their biological importance. The results were expressed as hazard ratio (HR) with their respective 95% confidence intervals (CI). For analysis of CVC infection, Cox regression adjustments were performed for time-dependent covariables (CVC time in days) until the

occurrence of the patient's first event. The other catheters inserted after the occurrence of CLABSI were excluded from this analysis. The data were stored and analyzed in the statistical programs SPSS 22.0 (IBM SPSS Statistics for Windows, Armonk, NY) and R version 3.5.1 (Foundation for Statistical Computing, Vienna, Austria). In all analyses, a *P* value of <.05 was considered as statistically significant. The study was conducted in accordance with local regulations and with the current guidelines for observational studies [17]. All data were analyzed anonymously.

Results

We reviewed 181 medical charts of patients who received PN between January 2016 and December 2017 (24 consecutive months). Sixteen patients were excluded leaving 165 patients and 247 CVCs (Figure 1).

Description of Study Cohort:

Table 1 summarizes the main characteristics of the included patients. Most patients were males, 56.3 ± 16.6 years old, overweight, median Charlson index was 4 and the most frequent comorbidity was cancer. Mean nutritional prescription, caloric and proteic, was adequate. Overall mortality rate was 24.8%. The most prevalent outcome was any infectious complication during PN administration, mainly due to abdominal infection.

Clinical Outcomes:

Table 2 summarizes the findings associated with CLABSI. There were 28 episodes of CLABSI (11.3% of 247 CVCs), but some events occurred in the same patient. At least one episode of bloodstream infection occurred in 24 patients (14.5% of 165 patients). Considering the time used for each CVC, the CLABSI

index was 6.47 per 1000 CVC-days. In the univariable analysis, CLABSI was associated with longer hospitalization time, longer PN time, longer CVC time, catheter insertion performed by a surgeon or a surgical resident, and procedures performed outside the ICU. No association was found with total calories of PN, proportion of macronutrients, hyperglycemia, supplemental PN, use of ultrasound or comorbidities at the beginning of PN. Furthermore, no CLABSI occurred in less than 5 days of CVC use (median of 15 days), and using a recently inserted device (with less than 48 hours of use) when starting PN was not associated with a lower rate of CLABSI. In an extended time-dependent Cox regression, no variable was associated with a higher risk of CLABSI in the univariable and multivariable analysis **(Table 3).** Additional information about the 247 CVC insertion procedures is available in **Supplementary Table**.

About the CLABSI epidemiology, Coagulase-negative staphylococci were present in 13 cases (46.4%), followed by fungal infections (*Candida*) in eight cases (28.6%) and *Staphylococcus aureus* in two cases (7.1%). *Klebsiella*, *Enterococcus*, *Pseudomonas*, *Enterobacter*, and *Escherichia* were responsible for one case of CLABSI each (3.6%). The median time for blood culture positivity in CLABSI cases was 13.9 hours (12-24 hours) for peripheral blood culture and 12.2 hours (9.9-19.8 hours) for blood cultures collected from the PN pathway.

Overall mortality rate was 24.8% in our study. Higher Charlson index, starting PN in ICU, development of any infection during PN administration and development of abdominal infection during PN administration were related to death (**Table 4**). In the multivariate analysis with these variables, only the Charlson comorbidity index remained statistically significant associated with mortality (HR 1.175; CI 1.052-1.312; p = .004).

Discussion

In our study, we analyzed a large sample of patients submitted to PN over a two-year period in a university hospital of the South of Brazil. As far as we know, this is one of the largest cohorts identified in the international literature that analyzed patients receiving PN both in the general ward and in the ICU settings. The rate of infectious complications in these individuals is high. Patients who needed PN had a higher incidence of CLABSI compared to patients with CVC and without PN in the literature, [18, 19] but no characteristics of PN studied were associated with CLABSI and additional days of PN did not increase the rate of CLABSI in the multivariable analyses in our study.

In an earlier study conducted in the same hospital almost twenty years earlier [10], PN was associated as an independent factor in the multivariate analysis for CLABSI. That study differs from the present one by inclusion of only ICU patients, and because microbiological analyses of all patients (blood culture or catheter tip) were performed. The association between PN and infection could be due to the colonization of the device. Probably for the same reason, a twofold higher rate of CLABSI per 1000 catheter days was identified in comparison with the current study, although improvements in procedures and in the catheter care that have been established over time may have also influenced this difference.

The high incidence of CLABSI found in our study (6.47 per 1000 CVC-days or 11.7% of all CVCs) when compared to patients with CVC and without PN in the literature [18-20] is still within the range (which reaches 18.8 per 1000 CVC-days) of the international literature for PN-associated CVC infection [6]). In a time-dependent Cox regression, PN time was not an isolated factor that could justify a higher incidence of CLABSI in this population. It is difficult to identify reasons

for this incidence, since the study was conducted in a university hospital accredited by the Joint Commission [21] and specific bundles for CVC care are available in our hospital. Nevertheless, Brazil is an emerging country and data about catheter infection, especially in patients receiving PN, are scarce.

Dissanaike [22] found an association between CLABSI and a higher rate of total calorie infusion, which was not observed in our cohort. Most of the patients in Dissanaike's study received more than 30-40 kcal/kg/day, different from the current study, where the local protocol encouraged a goal of 22-25 kcal/kg/day and few patients received more than 30 kcal/kg/day, in accordance with recent guidelines [3]. We believe that such findings indicate that avoiding hyperalimentation may reduce the rate of CLABSI and other unfavorable outcomes, as already demonstrated by studies that limited total calories and compared parenteral and enteral nutrition using the same caloric target [4]. One possible explanation for our high CLABSI rate is the use of two-in-one bags separated from intravenous lipid emulsion that are supposed to be associated with an increased risk of infection, through CVC manipulation. However, this evidence is still limited and not sufficient to endorse or refute such an association [23].

The present study did not identify lower rates of CLABSI when a new CVC was installed after indication of PN, thus not justifying the need for a new device or replacement of the CVC when initiating such therapy. Other catheter-related factors, such as the number of lumens, were also not associated with chance of infection in our study, although the analysis was not robust because of the low prevalence of mono-lumen catheters (less than 5%) used in our hospital. Therefore, it is impossible to refute this association found in the literature [24],

and although recommended, there is a paucity of evidence regarding PN-dedicated lumens [25] .

Our mortality rate is high, and the age-adjusted Charlson comorbidity index indicates that our sample of patients is sicker than population in other PN studies, probably justifying the higher mortality [26, 27]. This comorbidity metrics is the most commonly studied prognostic measure of illness burden in clinical research [28] and is probably related to increased rates of chronic disease and mortality [29-31]. Our study failed to identify prolonged hospitalization or PN time as isolated factors to justify this rate. Only greater number of comorbidities was associated with mortality in the multivariate analysis.

Among the limitations, the study methodology does not allow for cause-effect inference, although it is possible to generate hypotheses. Multivariable analysis and logistic regression were performed to mitigate the bias of confusion. Furthermore, our high rate of infection does not invalidate the analysis that CLABSI is not associated with specifics PN or vascular access characteristics. In addition, the retrospective design may hinder outcome recovery and related factors due to underreporting in the medical records. To attenuate the underreporting, we chose laboratory results and the outcome of hospitalization (death or discharge) as the main outcomes. The study was not powered to detect mortality difference a priori, and this aspect should be considered when analyzing data.

The exclusion of LTC and PICC of the analyses is also a limitation. LTC may lead to underreporting due to their out-of-hospital use and possibility of lack of notification or even occurrence of an outcome in another institution. It has already been stated that PICC were used in the hospital during the study only in

experimental situations and they were not analyzed because of the possibility of bias due to differentiated care involving a new technology. As a mitigating factor, less than ten of these devices (seven LTC and two PICC) were used for PN in the hospital in this period (3.6% of all catheters used for PN), possibly not affecting the results.

In conclusion, patients who needed PN in our study had a considerable rate of CLABSI and other infectious complications. No variable was associated with higher risk of CLABSI in the univariable and multivariable analysis after adjustment for catheter time. The mortality rate is high and it was not associated with PN in multivariable analyses, only with Charlson comorbidity index.

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Figure 1: Flowchart

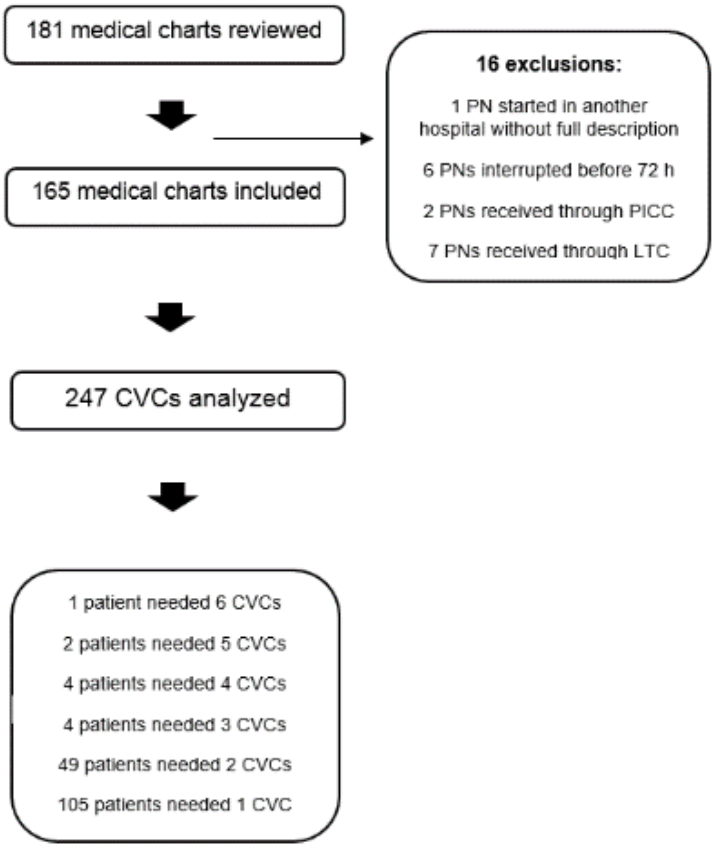

Fig 1. **Flowchart of Included and Excluded Patients.** CVC: central venous catheter; LTC, long-term catheter; PICC, peripherally inserted central catheter

Table 1: Characteristics of the Included Patients (n = 165):

Characteristics	Value
Age (years)	56.3 (± 16.6)
Male	92 (55.8%)
Weight (kg)	70.15 (± 16.6)
BMI (kg/m²)	25.42 (± 5.6)
Surgical admission	132 (80%)
Abdominal surgery	119 (72.1%)
PN started in the ICU	71 (43%)
Hospitalization time (days)	43 (27.5-64.5)
Charlson (comorbidity index)	4 (2-6)
SAPS 3 ¶	63.4 (± 14.5)
SOFA ¶	5 (3-7)
Vasoactive drugs ¶	21 (12.7%)
PN time (days)	15 (9-25)
Total PN	125 (75.7%)
Supplemental PN	40 (24.2%)
Comorbidities	
DM	35 (21.2%)
Coronary artery disease	16 (9.7%)
Heart failure	6 (3.6%)
Stroke	16 (9.7%)
Pulmonary disease	20 (12.1%)
Hepatic disease	8 (4.8%)
Cancer	73 (44.2%)
Chronic kidney disease	13 (7.9%)
PN daily prescription	
Energy (kcal)	1598 (± 423.3)
Calories (kcal/kg)	25.2 (20.2-27.6)
Protein (g/kg)	1.5 (1.24-1.61)
Glucose (g/kg)	3.08 (2.52-3.52)
Lipids (g/kg)	0.8 (0.58-0.91)
Outcomes	
Mortality	41 (24.8%)
Hyperglycemia	62 (37.6%)
Any infection	107 (64.8%)
Pulmonary infection	28 (17%)
Abdominal infection	60 (36.4%)
Operative wound infection	7 (4.2%)
Urinary infection	9 (5.5%)
Bacteremia not related to CVC	7 (4.2%)
CLABSI	24 (14.5%)
Fungemia	12 (7.3%)

N represents the number of patients (and percentage). Mean (± standard deviation) or median (interquartile range). BMI, body mass index; ICU, intensive care unit; SAPS 3, simplified acute physiology score 3; SOFA, sequential organ failure assessment; PN, parenteral nutrition; DM, diabetes mellitus; CVC, central venous catheter; and CLABSI, central line–associated bloodstream infection. ¶ Only collected in the 71 patients who started PN in the ICU.

Table 2: Univariable Analysis for Evolution to CLABSI at Hospitalization

Variables:	CLABSI (24 patients)	No-CLABSI (141 patients)	*P*
Age (years)	55.9 ± 16.1	56.4 ± 16.7	.77
BMI (kg/m²)	26.4 ± 5.7	25.2 ± 5.6	.36
Charlson (comorbidity index)	5.5 (2-6)	4 (2-6)	.29
Postoperative	18 (75%)	113 (80.1%)	1
Hospitalization time (days)	66 (53.5-82)	38 (27-59)	.0001
PN time (days)	30 (11.5-43)	14 (9-23)	.003
DM	5 (20.8%)	30 (21.3%)	1
Hyperglycemia	8 (33.3%)	54 (38.3%)	.81
PN started in ICU	9 (37.5%)	61 (43.9%)	.719
Supplemental PN	2 (8.3%)	38 (27%)	.09
Energy (kcal/day)	1537 ± 402.7	1608 ± 427	.448
Proportion of calories from glucose (%)	45 (42 - 47.5)	45 (42 - 48)	.74
Procedure performed by a surgeon ¶ †	81 ± 7.9% (61-92%)	56 ± 3.7% (49-64%)	.025
Procedure performed in ICU †	16 ± 7.4% (6-36%)	39 ± 3.6% (32-46%)	.03
CVC time (days) †	20.6 ± 1.6 (17.4-23.7)	17.27 ± 0.8 (15.7-18.8)	.034
Double-lumen †	96 ± 3.5% (78-100%)	95 ± 1.5 (91-97%)	.741
Subclavian-site †	39 ± 8.5% (24-56%)	38 ± 3.3% (32-45%)	.933
Ultrasound-guided †	37 ± 8.3% (23-54%)	52 ± 3.6% (45-59%)	.123
PN infused in a recently inserted (< 48h) CVC †	82 ± 7.5% (63-93%)	77 ± 2.8% (71-82%)	.55

BMI is body mass index; ICU, intensive care unit; PN, parenteral nutrition; DM, diabetes mellitus; CVC, central venous catheter; and CLABSI, central line–associated bloodstream infection. The cells represent N (%), mean ± SD or median (interquartile range). † Estimated marginal mean ± standard error and 95% Wald confidence interval, through analysis by GEE (log-gamma distribution). ¶ Surgeon or a surgical resident.

Table 3: Evolution to CLABSI in a time-dependent Cox regression

	HR	CI	p value
Univariable time-dependent			
Procedure performed by a surgeon ¶	2.235	0.82-6.07	.11
Number of previous CVC needed for PN	1.148	0.42-1.76	.7
PN time until current CVC	1.002	0.94-1.05	.92
Total time of PN	0.991	0.99-1.02	.15
Hospitalization time until current CVC	1.001	0.97-1.02	.91
Total time of hospitalization	0.995	0.99-1.01	.42
Multivariable time-dependent			
Procedure performed by a surgeon ¶	2.215	0.81-6.01	.11
Total time of PN	1.009	0.99-1.02	.16

Extended Cox model for time-dependent covariates, through "R" survival package. HR: Hazard Ratio; CI: 95% confidence interval. R square = 0.019. Concordance = 0.566. Likelihood ratio test = 4.38. Wald test 4.28. Logrank test 4.54 p = 0.1. ¶ Surgeon or a surgical resident.

Table 4: Univariable Analysis for Evolution to Death at Hospitalization

Variables:	Death (41 patients)	Discharge (124 patients)	*P*
Age (years)	60.2 ± 17.1	55.06 ± 16.3	.087
BMI (kg/m²)	24.1 ± 3.9	25.8 ± 6	.099
Charlson (comorbidity index)	5 (4-7)	3 (2-6)	.001
Postoperative	33 (80.5%)	99 (79.8%)	1
Hospitalization time (days)	43 (29-67)	43 (27-63.75)	.76
PN time (days)	17 (9-25)	15 (9-24.5)	.815
DM	12 (29.3%)	23 (18.5%)	.21
Hyperglycemia	19 (46.3%)	43 (34.7%)	.25
PN started in ICU	26 (63.4%)	45 (36.3%)	.003
Any infection during PN	33 (80.5%)	74 (59.7%)	.026
Abdominal infection during PN	21 (51.2%)	39 (31.5%)	.036
Pulmonary infection during PN	10 (24.4%)	18 (14.5%)	.22
CLABSI during PN	5 (12.2%)	19 (15.3%)	.8
Supplemental PN	7 (17.5%)	33 (26.6%)	.3
Calories infused / day (kcal)	1521.5 ± 383.6	1623.4 ± 434.1	.18
Proportion of calories from glucose (%)	45 (43 – 48)	45 (41.2 – 48)	.79

BMI represents body mass index; ICU, intensive care unit; PN, parenteral nutrition; DM, diabetes mellitus; CVC, central venous catheter; and CLABSI, central line–associated bloodstream infection. The cells represent N (%), mean ± SD or median (interquartile range).

Supplementary Table: Characteristics of the 247 CVC insertion procedure

Procedure	n = 247
Procedure performed by a physician with training in general surgery	149 (60,3%)
Procedure performed in the ICU	88 (35,6%)
PN infused in a recently inserted CVC (less than 48h of use)	192 (77,7%)
CVC time (days)	14 (9 – 23)
Executor of procedure	
First year resident	105 (42,5%)
Second year resident	23 (9,3%)
Third year residente	40 (16,2%)
Fourth year residente	7 (2,8%)
Staff	31 (12,6%)
Not identified	41 (16,6%)
Catheter insertion technique	
Ultrasound guided puncture	123 (49,8%)
Anatomical landmarks puncture	87 (35,2%)
Guide wire Exchange	17 (6,9%)
No description	20 (8,1%)
Catheter (regarding the number of lumen)	
Single-lumen	12 (4,9%)
Double-lumen	232 (93,9%)
Triple-lumen	3 (1,9%)
Puncture Site	
Subclavian	95 (38,5%)
Jugular	147 (59,5%)
Femoral	4 (2,1%)
Complications	
CLABSI	28 (11,3%)
Mechanical complication (pneumothorax, arterial punction…)	6 (2,4%)

N: number of patients; %: percentage; IQR: interquartile range; CVC: central venous cateter; ICU: intensive care unit; PN: parenteral nutrition; CLABSI: central line associated bloodstream infection

Capítulo 3

Artigo 2

Mortality, overall and specific infection complication rates in patients who receive parenteral nutrition: systematic review and meta-analysis with trial sequential analysis

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Abstract

Background: Parenteral nutrition is an available option for nutritional therapy and is often required in the hospital setting to overcome malnutrition.

Objective: The aim of this study was to assess whether parenteral nutrition is associated with an increased risk of mortality or infectious complications in all groups of hospitalized patients compared to those receiving other nutritional support strategies

Design: For this systematic review and meta-analysis MEDLINE, EMBASE, Cochrane Central, SCOPUS, ClinicalTrials.gov and Web of Science were searched for randomized controlled trials and observational studies with parallel groups that explored the effect of parenteral nutrition on mortality and infectious complications, published until March 2021. Two independent reviewers extracted the data and assessed the risk of bias. Fixed effects meta-analysis was performed to compare the groups from randomized controlled trials. Trial sequential analysis was used to identify whether the results were sufficient to reach definitive conclusions.

Results: Of the 83 included studies that compared patients receiving parenteral nutrition to those receiving other strategies, 67 randomized controlled trials were included in the meta-analysis. Parenteral nutrition was not associated with a higher risk of mortality (relative risk = 1.01, 95% confidence interval [0.95, 1.07]). On the other hand, parenteral nutrition was associated with a higher risk of infectious event (relative risk = 1.23, 95% confidence interval [1.12, 1.36]). Parenteral nutrition was specifically associated with abdominal infection and catheter infection. The trial sequential analysis showed that there were sufficient

data to make numerical conclusions about mortality, any infectious event and abdominal infectious complications.

Conclusions: This study suggests that although parenteral nutrition is not associated with greater mortality in hospitalized patients, it is associated with infectious complications. Through trial sequential analysis, definite conclusions about survival and infection rates could be made.

Keywords: parenteral nutrition, hospital infection, mortality, nutritional support, infection.

Introduction

Parenteral nutrition (PN) is the provision of calories, amino acids, electrolytes, vitamins, minerals, trace elements and fluids via a parenteral route. It is an available option for nutritional therapy and is often required in the hospital setting to overcome malnutrition (1). Nourishing patients using means other than the alimentary tract was advocated and attempted for many decades before its successful achievement, requiring centuries of studies coupled with technological developments (2).

The first evidence that PN could provide nutritional support was demonstrated in Beagle puppies in 1966 and in humans in 1968 (3), but the first randomized controlled trials (RCT) were only published in the 1980s. These studies analyzed the impact of using this route in surgical and trauma patients, and did not have enough power to detect harm or benefit due to their small sample size (4, 5). Over time, new studies on PN have been published and other clusters have been analyzed, such as patients with pancreatitis, evaluated by the late 1990s (6), and critically ill patients in the 2000s (7). Most studies suffered from a low number of patients allocated to each group, as well as a high rate of bias.

Besides critically ill patients and those with severe acute necrotizing pancreatitis, PN is mainly prescribed to patients with contraindications or intolerance to enteral nutrition (8) in several settings, such as perioperative nutrition in patients with moderate to severe malnutrition, acute exacerbations of Crohn’s disease, gastrointestinal fistulas and extreme short bowel syndrome (1). However, as more evidence has been collected, PN has been associated with several important adverse effects including infections (9), metabolic effects such

as hyperglycemia (10) and refeeding syndrome (11), and complications related to venous access (12, 13). Some systematic reviews on specific populations published over the two last decades and meta-analysis have concluded that enteral nutrition should be the preferred route of nutritional support due the significantly lower incidence of infections, although no survival benefit has been shown (14-16).

Until now, the impact of important confounding factors, such as glycemic control, disease severity scores and energy intake, in association with PN outcomes is not fully understood. Therefore, the aim of this study was to assess whether PN is associated with an increased risk of mortality or infectious complications in all groups of hospitalized patients receiving PN compared to those receiving other nutritional support strategies. This systematic review includes recent studies about PN, sensitivity analysis according to confounders, and the use of trial sequential analysis (TSA), a novel methodology in PN reviews.

Material & Methods

This systematic review was carried out using a protocol constructed according to the Cochrane Handbook (17) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (18). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the number CRD42018075599.

Search strategy

We searched MEDLINE, EMBASE, Cochrane Central, SCOPUS, Clinical Trials and Web of Science to identify RCTs and observational studies that

reported outcomes related to PN through March 2021. A manual search was also performed in the reference lists of included articles and recent reviews on the topic (7,14,15,19). The full search strategy is available in the supplementary material (Supplementary Methods: Full search strategy). All eligible trials were considered for review regardless of their year of publication. Articles were limited to English, Portuguese and Spanish languages, although the literature search was not confined to articles written in these languages.

Study selection, inclusion and exclusion criteria

The inclusion criteria were as follows: (1) RCTs or observational studies with a parallel group in hospitalized patients, (2) parenteral nutrition versus any comparator, and (3) mortality or infection data reported. Trials were excluded if they considered parenteral nutrition as a solution without all these components: protein, lipids, and carbohydrates, as well as home parenteral nutrition studies. Definitions of total PN or supplemental PN were performed according to patient´s intake status: fasting or any oral or enteral ingestion, respectively. For trials with more than one publication involving the same study population, only the most recent publication was included. Studies were separated into subgroups. Wherever possible, we classified studies into one of the following groups according to patient characteristics: pancreatitis, surgical, trauma, or intensive care unit (ICU). The outcomes of interest were mortality, any infectious event (any infection without topographic definition specified by the selected article) and the rate of specific infections: pneumonia, abdominal infection (peritonitis, infected pancreatic necrosis or intraabdominal abscess) and catheter infection, as specified by the methodology of the selected paper.

Data extraction and quality assessment

All citations retrieved from electronic databases were imported into EndNote software version X7 (Clarivate Analytics, Philadelphia, PA, USA). Two independent investigator (PHC and JS) selected studies based on title and abstract. Studies that met the inclusion criteria, or those with abstracts that lacked information important for the final decision, were included in the full-text analysis. Both investigators analyzed the full-text articles and extracted data. A third reviewer (LVV) resolved any disagreements.

Data from the included studies were independently extracted by the same two reviewers using a standardized data extraction form. Extracted data included the following: first author's name, year of publication, number of participants, details of the study design, trial duration, patient characteristics, diet characteristics, and outcomes.

Risk of bias in individual studies

The Cochrane Collaboration tool for risk of bias (20) was used for randomized trials. Regarding the risk of bias, we considered a potential conflict of interest as the 'other' domain, evaluated by the same two reviewers. The risk of bias for each domain was classified as high, low or unclear. For observational studies (only included in qualitative synthesis), we used the Newcastle–Ottawa scale (21). Studies were assessed with stars in the selection domain (0–4 stars), comparability (0–2) and outcome (0–3). Studies were classified as good, fair or poor quality according to the number of stars.

Quality of the meta-analysis

The quality of the meta-analysis was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (22), including factors that may decrease (e.g. methodological quality, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias) or increase (e.g. large magnitude of effect, reduction or spurious effect due to plausible confounding factors and dose-response gradients) the quality of evidence. Each evaluated factor was rated as high, moderate, low or very low. Using this approach, we considered a serious risk of bias when an individual study had more than three unclear or one high risk of bias, and imprecision was defined as a wide confidence intervals in meta-analysis (>.5 or >2.0 [very serious]).

Data analysis

For the meta-analysis of RCTs, we compared the events of interest in patients randomized to receive PN versus non-PN as a control strategy (enteral nutrition, oral nutrition or no nutrition). Descriptive data from the qualitative analysis were presented as they were published (mean or median), with the standard deviation or range. The outcomes with binary data were summarized with relative risk (RR), and direct meta-analysis was used to compare the PN group to the control group. We calculated the pooled RR using the Mantel–Haenszel estimator, with fixed effects. Heterogeneity was assessed using the Cochran Q test (p-value of 0.1 was considered statistically significant) and the I^2 test (values greater than 50% were considered to indicate elevated statistical heterogeneity).

We performed the TSA meta-analysis technique to evaluate the statistical reliability of the findings and to determine whether sufficient data was available to make definitive conclusions. We performed the analysis defining power as 80%, type I error as 5% and the expected relative difference between groups as 20%. TSA combines features from cumulative meta-analysis with sample size calculation and interim analysis, creating a Z-curve and boundaries to identify benefit, harm or futility. If the curve crosses one of the boundaries or reaches the optimal sample size line, definitive conclusions can be assumed (for previously defined difference, heterogeneity, and type I and II errors) (23, 24). In summary, the results of the TSA specify whether the current results and amount of information are enough to make definitive conclusions.

Publication bias was evaluated with a visual inspection of funnel plots and with Begg's and Egger's tests, as appropriate. If a small study bias was identified, we then performed a trim-and-fill computation to explore the effect of missing studies on the outcomes.

The analysis were performed using RevMan software version 5.3 (Cochrane IMS, Oxford, UK) and Stata version 13.0 (StataCorp). The TSA was performed with TSA software version 0.9.5.10 Beta (Centre for Clinical Intervention Research Department, Copenhagen, Denmark).

Sensitivity analysis

Specific sensitivity analysis were performed for all studied outcomes. The first one explored whether the selection of only low bias studies would affect the result. The second one analyzed whether the selection of studies that specified the gravity score and glycemic control would change the conclusions regarding

the outcomes. The last analysis was planned according to the time of publication (before and after year 2010). Subgroup analysis was performed to further explore whether the treatment effect of either protein or total calories was associated with significant differences across the study groups. We also hypothesized that the possible negative treatment effect of PN on mortality and infectious complications could be related to overfeeding; therefore, we separated the studies into three subgroups: similar number of calories and protein in both groups, higher amount of calories and protein in the parenteral nutrition group, or not specified. We used the reported significance level for caloric intake across groups within each study to allocate studies to each subgroup. Exploratory analyses were performed when necessary.

Results

Search results

The study selection process is presented in **Figure 1**. In summary, 2397 references were identified, 1790 titles and abstracts were reviewed, and 83 full-text articles were included in the final analysis. The reasons for full-text exclusions are listed in Supplementary Table 1: Exclusions.

Characteristics of the included trials

Study characteristics (first author, year, study design, sample demography, intervention and control characteristics, intervention duration, outcomes reported, follow up and glycemic control) are presented in Supplementary Table 2.

Overall, these studies included a total of 16 375 patients. The mean age ranged from 27 to 70 years. The most studied subgroup was ICU patients, with 36 studies. Other specific populations included pancreatitis, surgical, trauma, colitis, advanced cancer, burn-induced invasive fungaemia and hospitalized patients receiving artificial nutrition. Of the studies, 67 were RCTs and 16 were observational studies (nine prospective and seven retrospective). The most common intervention was total PN (used in 65 studies), with supplementary PN used in 10 studies and both interventions used in eight studies. The most common control was enteral nutrition (65 studies), followed by fasting (eight studies), oral nutrition (eight studies) or more than one control (two studies). The interventions lasted between 4 and 32.8 days. A summary of severity scores, calories and protein received and glycemic control is available in Supplementary Table 3.

Risk of bias across studies

Regarding the quality of studies, most RCTs were unblinded, and half of them were at unclear risk of selection bias due to allocation concealment (Supplementary Figure 1 and 2). Regarding the observational studies, only three studies were classified as poor quality and 12 studies considered good quality (Supplementary Table 4).

Mortality

From the 72 studies (14 406 patients and 3967 events) that reported this outcome, patients who received PN had a mortality rate of 29.1% (1993 events in 6848 patients) and patients from the control group had a rate of 26.1% (1974

events in 7558 patients). These and other relevant outcomes of the included trials are summarized in Supplementary Table 5.

When observational studies were excluded from the quantitative analysis, 59 studies performed a comparison between PN and any comparator and showed no increased risk of mortality, with an RR of 1.01 (95% CI [0.95, 1.07). Statistical heterogeneity was present, with low inconsistency (I^2 = 24%, P = 0.06; **Figure 2**). Publication bias was detected in the Egger test, but the trim-and-fill computation did not change the results (Supplementary Results 1A). TSA analysis calculated an optimal sample size of 10 499 patients, but reject a RR of 20% between groups, as the futility boundary was reached (Supplementary Results 2A). The sensitivity analysis did not change the results of either comparison (Supplementary Results 3A).

In the GRADE evaluation (Supplementary Table 6), a 1-point downgrade was applied due to performance and detection bias. The quality of evidence was considered moderate as the remaining factors were considered to be of adequate quality, with no relevant statistical heterogeneity, confidence intervals not excessively wide and no publication bias that invalidated the analysis.

Any infectious event

From the 44 studies (7569 patients and 1788 events) that reported this outcome, patients who received PN had an infection rate of 27.4% (992 events in 3617 patients) and patients in the control group had a rate of 20.1% (797 events in 3952 patients).

When observational studies were excluded from the quantitative analysis, 37 studies performed a comparison between PN and any comparator and

showed an increased risk of infection, with an RR of 1.23 (95% CI [1.12, 1.36]). Statistical heterogeneity was present, with low inconsistency (I^2 = 24%, P = 0.10; **Figure 3**). Publication bias was not identified (Supplementary Results 1B), and the Begg and Egger tests were not significant. TSA analysis calculated an optimal sample size of 7061 patients and the harm boundary was reached, with a higher infection risk of PN confirmed by TSA (Supplementary Results 2B). The sensitivity analysis did not change the results of either comparison (Supplementary Results 3B). Regarding the GRADE evaluation (Supplementary Table 6), a 1-point downgrade was applied due to performance and detection bias. The quality of evidence was considered moderate.

Pneumonia

From the 39 studies (9902 patients and 1155 events) that reported this outcome, patients who received PN had a pneumonia rate of 12.5% (555 events in 4435 patients) and patients in the control group had a rate of 10.9% (600 events in 5467 patients).

When observational studies were excluded from the quantitative analysis, 34 studies performed a comparison between PN and any comparator, showing no increased risk of pneumonia, with an RR of 1.10 (95% CI [0.98, 1.23]). Statistical heterogeneity was not present, with low inconsistency (I^2 = 16%, P = 0.20; Supplementary Figure 3). Publication bias was not identified (Supplementary Results 1C), and the Begg and Egger tests were not significant. TSA analysis calculated an optimal sample size of 11 677 patients, and the optimal sample size, harm boundary and futility boundary were not reached (Supplementary Results 2C). The sensitivity analysis did not change the results

of either comparison (Supplementary Results 3C). In the GRADE evaluation (Supplementary Table 6), a 1-point downgrade was applied due to performance and detection bias. The quality of evidence was considered moderate.

Abdominal infection

From the 26 studies (2973 patients and 349 events) that reported this outcome, patients who received PN had an abdominal infection rate of 15.7% (231 events in 1469 patients) and patients in the control group had a rate of 7.8% (118 events in 1504 patients).

When observational studies were excluded from the quantitative analysis, 24 studies performed a comparison between PN and any comparator and showed an increased risk of abdominal infection, with an RR of 2.02 (95% CI [1.63, 2.51). Statistical heterogeneity was not present, with low inconsistency (I^2 = 20%, P = 0.19;-Supplementary Figure 4). Publication bias was detected in the Egger test, but the trim-and-fill computation did not change the results (Supplementary Results 1D). TSA analysis calculated an optimal sample size of 10 317 patients and the harm boundary was reached, with a higher abdominal infection risk with PN confirmed by TSA (Supplementary Results 2D). The sensitivity analysis did not change the results of either comparison, but an exploratory analysis identified an association of abdominal infection with total PN, but not with supplementary PN (Supplementary Results 3D). Regarding the GRADE evaluation (Supplementary Table 6), a 1-point downgrade was applied due to performance and detection bias. Another 1-point downgrade was applied because the confidence interval was higher than 0.5, classifying the quality of evidence as low.

Catheter infection

From the 27 studies (7545 patients and 210 events) that reported this outcome, patients who received PN had a catheter infection rate of 4% (131 events in 3256 patients) and patients in the control group had a rate of 1.8% (79 events in 4289 patients).

When observational studies were excluded from the quantitative analysis, 24 studies performed a comparison between PN and any comparator and showed an increased risk of catheter infection, with an RR of 2.16 (95% CI [1.58, 2.93]). Statistical heterogeneity was not present, with low inconsistency (I^2 = 15%, P = 0.26; Supplementary Figure 5). Publication bias was detected in the Egger test, and the trim-and-fill computation changed the results, nullifying the significance (Supplementary Results 1E). TSA analysis returned an optimal sample size of 44 291 patients. Optimal information, futility boundary and the harm boundary were not reached (Supplementary Results 2E). The sensitivity analysis also changed the result, which was no longer statistically significant when only low bias studies were selected (Supplementary Results 3E). Regarding the GRADE evaluation (Supplementary Table 6), a 1-point downgrade was applied due to performance and detection bias. Another 1-point downgrade was applied because the confidence interval was higher than 0.5, and an additional 1-point downgrade was applied due to publication bias and the sensitivity analysis. In this case, the quality of evidence was considered very low.

Discussion

This systematic review evaluated mortality and infectious complications in 16 375 patients (83 RCTs and observational studies) who received nutrition support (PN versus others). We were able to perform a meta-analysis on 67 RCTs. PN was not associated with a higher risk of mortality or pneumonia. On the other hand, PN was associated with a higher risk of any infectious event. These analyses were determined to be of moderate quality. Also, PN was specifically associated with abdominal infection and catheter infection, with low and very low quality of evidence. There was no difference in the main results according to the publication date of the studies (newer vs. older studies) but when only low bias studies were selected, catheter infection were not higher in the PN group.

Compared to previous reviews (14-16), we were able to identify a higher number of studies, and consequently, include more patients and events, adding strength to the evidence. Our results are in agreement with previous studies that indicate that PN did not increase mortality rates but it increases the risk of infectious complications. Our sample size allowed us to explore potential sources of clinical heterogeneity through separate analysis of specific infection site, study populations and outcomes and through sensitivity analysis. We used TSA to verify our results, a novel methodology in nutrition reviews. Our TSA analysis showed that there were sufficient data to reach numerical conclusions about mortality, infection and abdominal infection rates, but also showed that the number of patients included was not enough to confirm or deny a reduction in relative risk of 20% for pneumonia and catheter infection.

Higher rate of catheter infection, as stated in other studies (16), seemed to be present only when low bias risk studies were analyzed together with high bias risk studies. We could also demonstrate a higher rate of abdominal infection, in addition to exploring that such findings are not specific to a particular condition as pancreatitis. Moreover, in studies using only supplementary PN (without bowel rest), there was no increased risk of abdominal infection. A possible explanation for abdominal infection is that bowel rest is associated with a disruption of the mucosal barrier structure and function, augmenting the inflammatory response to illness and leading to greater infectious complications (104, 105). The exploratory characteristic of these subgroup analyses included a small sample size. It would be interesting to evaluate the effect of bowel rest separate from PN to validate this conclusion.

Another hypothesis for the higher overall infectious complications associated with PN was proposed by a previous systematic review on critically ill patients (15), which found an association with greater nutritional support rather than the route itself. However, this result was not replicated in our current study. A higher caloric prescription was not associated with worse results in any analysis (Supplementary Results 3). Our larger sample size and diverse population selected could have influenced this finding.

The extension of our data search allowed us to perform publication date subgroup analysis without compromising the quality of our data. An important concern about our data was the comparison of older versus newer PN studies. In the past overfeeding was a common practice among physicians (4, 33). Nutrition practice changed considerably in the past 40 years (imunnonutrition, difference lipid formulations, hospital compounded vs industrial PN bags) as well as

glycemic control targets, catheter insertion techniques, antibiotic therapy, among others health care evolutions. We intended to preclude these biases evaluating the newer studies as a subgroup and we found similar results as previous meta-analysis (15). Likewise, the subgroup analysis of low risk bias studies (except for catheter infection) or those adjusted for disease severity and glycemic control did not alter the results of the whole meta-analysis. We believe that the whole group analysis were a strength of our paper since it could be a conservative bias (against PN), that could lead to worse results.

Some limitations of this review must be acknowledged. Firstly, most of the primary studies were not designed to assess mortality. As such, we missed some studies due to a lack of reporting. Also, we excluded studies that involved home parenteral nutrition, so it does not represent the outcomes of all clinical situations, especially more prolonged PN nutrition. In addition, despite the low statistical heterogeneity, we combined different comparators and types of nutrition, leading to possible clinical heterogeneity. We minimized this possibility by performing subgroup and sensitivity analysis. Moreover as the aim was to compare PN vs. non-PN we were unable to include some important studies, when they only compare strategies such as early vs late PN (both groups could receive PN) (106). The exclusion of articles in other languages and the lack of correspondence to authors may have meant some studies were missed, although the extensive manual search and publication bias analysis may have minimized this.

Conclusion

In conclusion, we demonstrated that while PN was not associated with greater mortality, it was associated with infectious complications. Through TSA,

we were able to reach definite conclusions about survival, any infectious event and abdominal infection; however, it was not possible to separate the effect of bowel rest from PN. Future high-quality RCTs are needed to differentiate whether parenteral nutrition without bowel rest (supplementary parenteral infusion) would still be associated with infectious complications.

PHC, and LVV designed research; PHC and JS conducted research; PHC, LVV analyzed data; PHC, LVV wrote the paper; PHC had primary responsibility for final content. All authors read and approved the final manuscript. The authors report no conflicts of interest.

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Figure 1. Study flowchart.

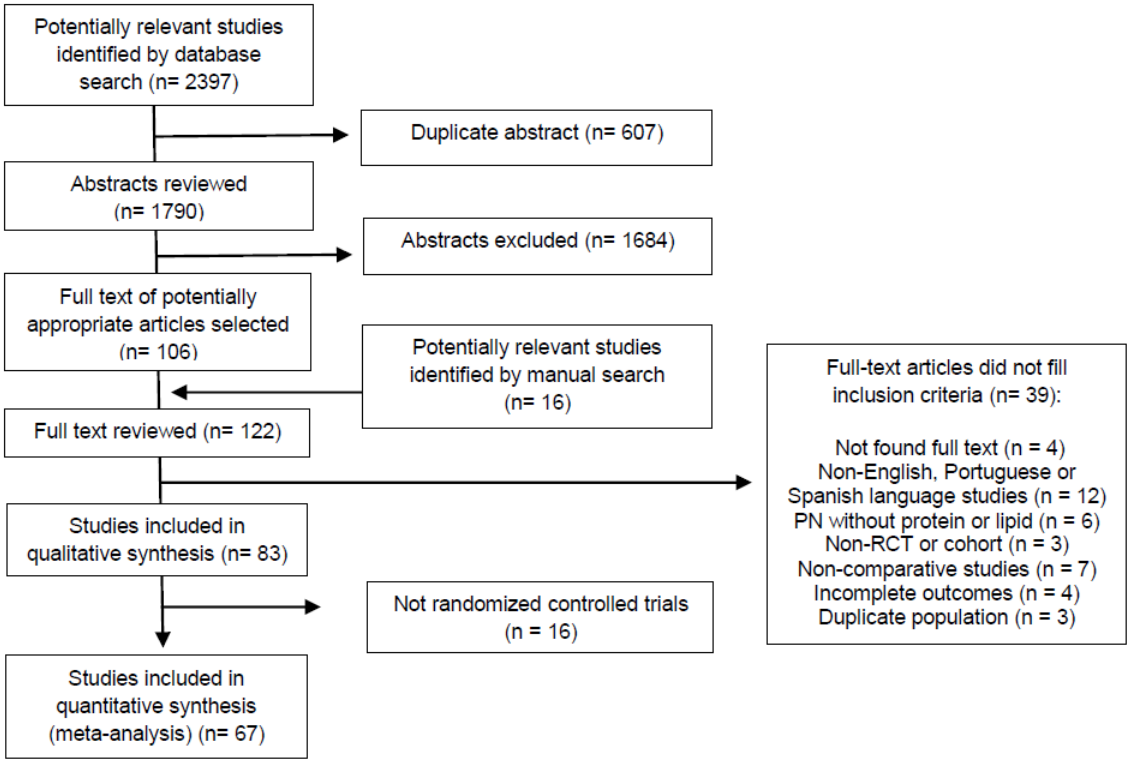
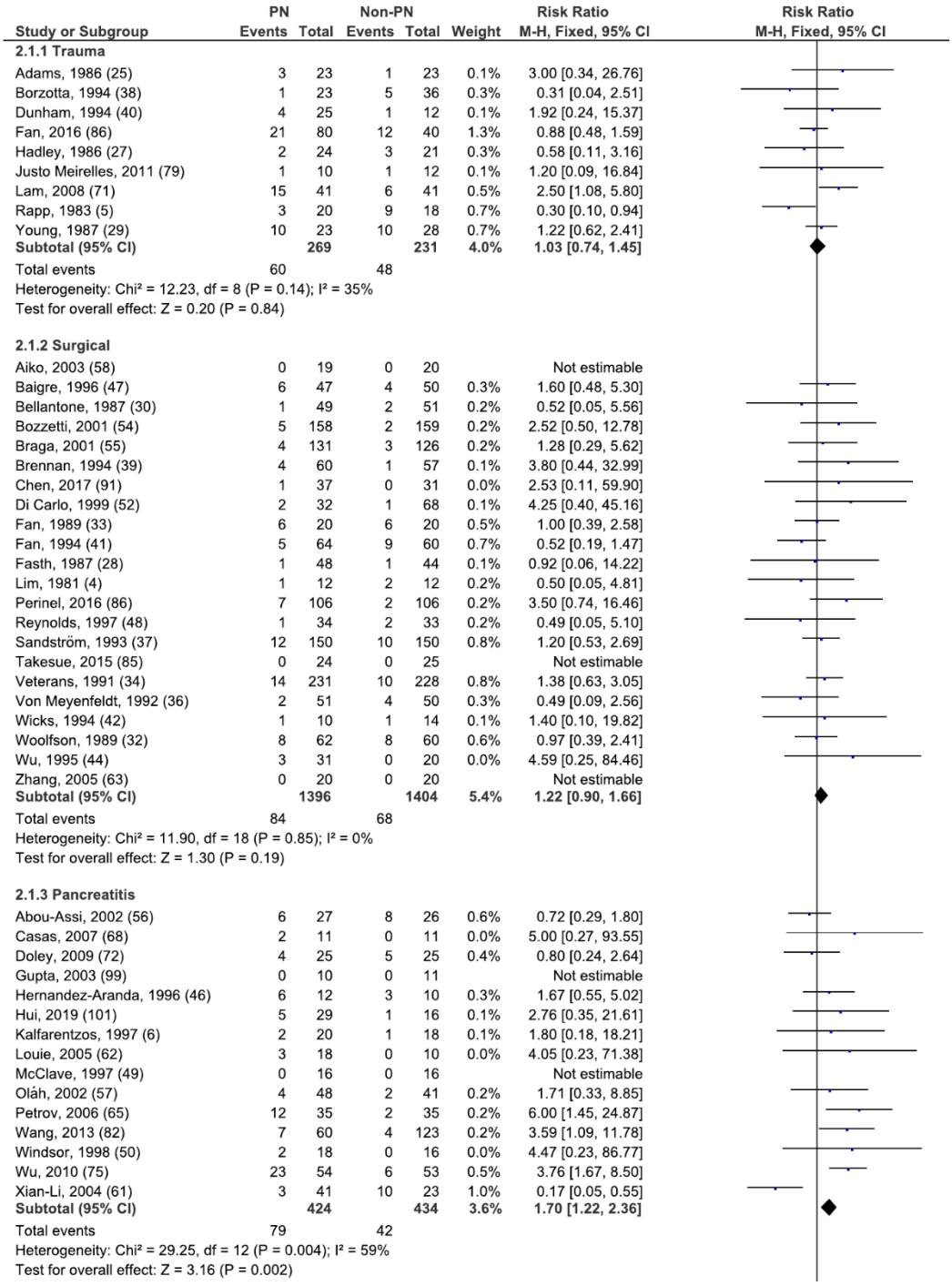


Figure 2. Forest plot for mortality in studies comparing parenteral nutrition (n = 59 RCTs) versus non-parenteral nutrition, stratified by study population. Fixed effects model of relative risk (95% confidence interval



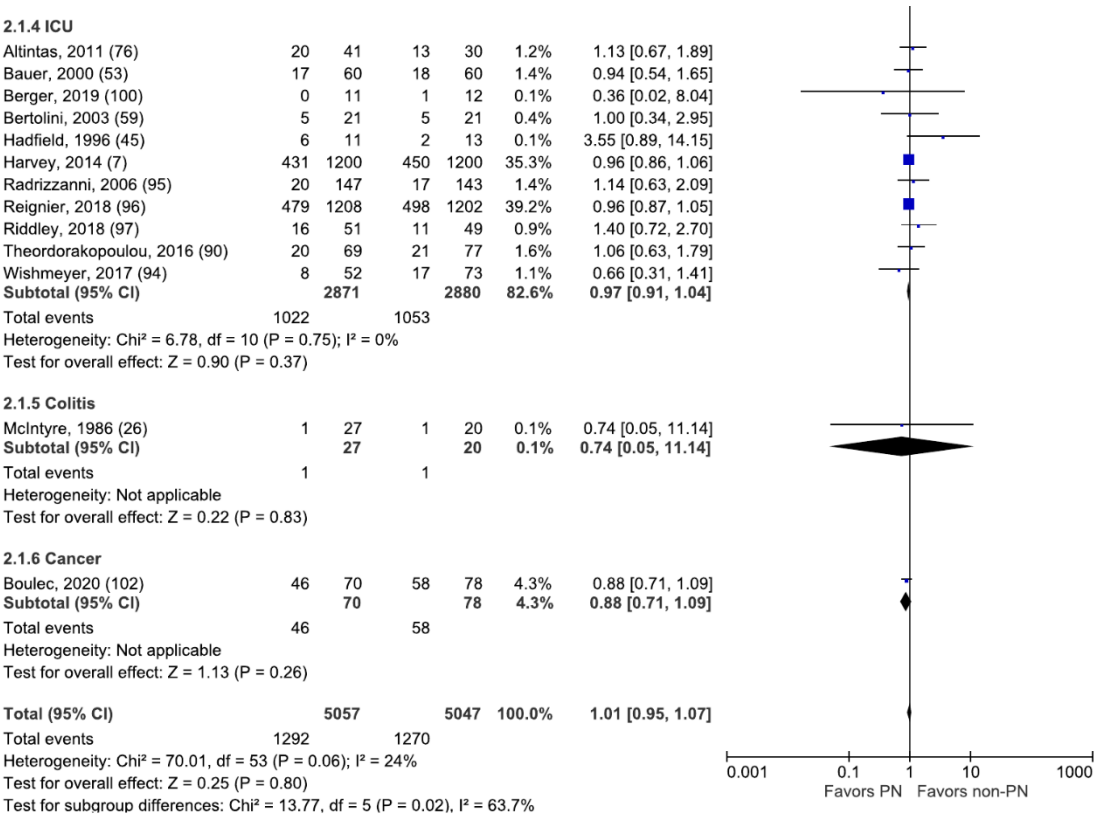
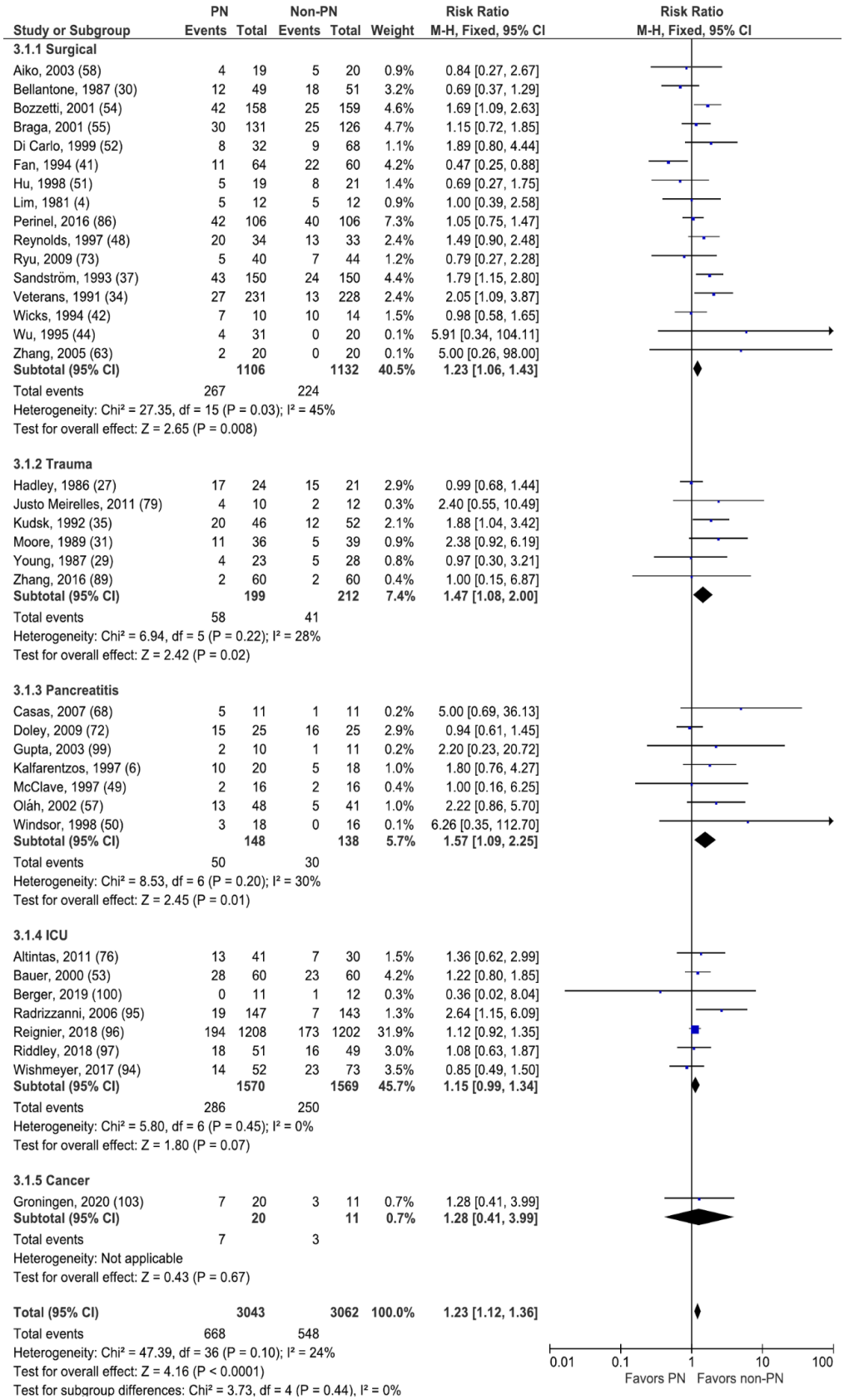

2.1.4 ICU
Altintas, 2011 (76) 20 41 13 30 1.2% 1.13 [0.67, 1.89]
Bauer, 2000 (53) 17 60 18 60 1.4% 0.94 [0.54, 1.65]
Berger, 2019 (100) 0 11 1 12 0.1% 0.36 [0.02, 8.04]
Bertolini, 2003 (59) 5 21 5 21 0.4% 1.00 [0.34, 2.95]
Hadfield, 1996 (45) 6 11 2 13 0.1% 3.55 [0.89, 14.15]
Harvey, 2014 (7) 431 1200 450 1200 35.3% 0.96 [0.86, 1.06]
Radrizzanni, 2006 (95) 20 147 17 143 1.4% 1.14 [0.63, 2.09]
Reignier, 2018 (96) 479 1208 498 1202 39.2% 0.96 [0.87, 1.05]
Riddley, 2018 (97) 16 51 11 49 0.9% 1.40 [0.72, 2.70]
Theordorakopoulou, 2016 (90) 20 69 21 77 1.6% 1.06 [0.63, 1.79]
Wishmeyer, 2017 (94) 8 52 17 73 1.1% 0.66 [0.31, 1.41]
Subtotal (95% CI) 2871 2880 82.6% 0.97 [0.91, 1.04]
Total events 1022 1053
Heterogeneity: Chi² = 6.78, df = 10 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
2.1.5 Colitis
McIntyre, 1986 (26) 1 27 1 20 0.1% 0.74 [0.05, 11.14]
Subtotal (95% CI) 27 20 0.1% 0.74 [0.05, 11.14]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)
2.1.6 Cancer
Boulec, 2020 (102) 46 70 58 78 4.3% 0.88 [0.71, 1.09]
Subtotal (95% CI) 70 78 4.3% 0.88 [0.71, 1.09]
Total events 46 58
Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Total (95% CI) 5057 5047 100.0% 1.01 [0.95, 1.07]
Total events 1292 1270
Heterogeneity: Chi² = 70.01, df = 53 (P = 0.06); I² = 24%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Chi² = 13.77, df = 5 (P = 0.02), I² = 63.7%
0.001
0.1
1
10
1000
Favors PN
Favors non-PN

Figure 3. Forest plot for any infection event in studies comparing parenteral nutrition (n = 37 RCTs) versus non-parenteral nutrition, stratified by study population. Fixed effects model of relative risk (95% confidence interval).



Supplementary Methods: Full search strategy

Medline: 656 studies found in 2021, 03.

((((((Parenteral Nutrition) OR ("Parenteral Nutrition, Total"[Mesh] OR "Parenteral Nutrition Solutions"[Mesh] OR "Parenteral Nutrition"[Mesh]) NOT "Parenteral Nutrition, Home Total"[Mesh] NOT "Parenteral Nutrition, Home"[Mesh]))) AND ((((((("Adult"[Mesh]) OR Adult*[Title/Abstract]) NOT Child*[Title/Abstract]) NOT Infant*[Title/Abstract]) NOT Newborn*[Title/Abstract]) NOT Neonate*[Title/Abstract])) AND ((((((((((("Infection"[Mesh]) OR "Sepsis"[Mesh]) OR "Bacteremia"[Mesh]) OR "Candidemia"[Mesh]) OR "Hospital Mortality"[Mesh])) OR infection[Title/Abstract]) OR bacteremia[Title/Abstract]) OR sepsis[Title/Abstract]) OR candidemia[Title/Abstract]) OR mortality[Title/Abstract])) AND (((((("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]) OR ("Clinical Trial" [Publication Type] OR "Pragmatic Clinical Trial" [Publication Type])) OR "Observational Study" [Publication Type]) OR "Cohort Studies"[Mesh]) NOT "Case-Control Studies"[Mesh]) NOT "Case Reports" [Publication Type]) NOT "Review" [Publication Type])

SCOPUS: 321 studies found in 2021, 03.

(TITLE-ABS-KEY (total AND parenteral AND nutrition) AND TITLE-ABS-KEY (adults) AND TITLE-ABS-KEY (infection) OR TITLE-ABS-KEY (mortality) OR TITLE-ABS-KEY (bacteremia) OR TITLE-ABS-KEY (candidemia) OR TITLE-ABS-KEY (sepsis) AND TITLE-ABS-KEY (randomized AND controlled AND trial) OR TITLE-ABS-KEY (observational AND study) AND NOT TITLE-ABS-KEY (child) AND NOT TITLE-ABS-KEY (newborn) AND NOT TITLE-ABS-KEY (infant) AND NOT TITLE-ABS-KEY (home) AND NOT TITLE-ABS-KEY (case AND control) AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (case AND report))

Embase: 594 studies found in 2021, 03.

'adult'/exp NOT 'child'/exp NOT 'newborn'/exp AND 'parenteral nutrition'/exp NOT 'peripheral parenteral nutrition'/exp NOT 'home parenteral nutrition'/exp AND ('infection'/exp OR 'mortality'/exp OR 'bacteremia'/exp OR 'candidemia'/exp OR 'sepsis'/exp) AND ('randomized controlled trial'/exp OR 'observational study'/exp) NOT 'case control study'/exp NOT 'review'/exp NOT 'case report'/exp

Clinical Trials: 32 studies found in 2021, 03.

Completed, Terminated Studies | Studies With Results | parenteral nutrition | infection OR sepsis OR candidemia OR bacteremia OR mortality | Adult, Senior

Web of Science: 632 studies found in 2021, 03.

ALL=(parenteral nutrition OR total parenteral nutrition) AND TS=(infection OR sepsis OR candidemia OR bacteremia OR mortality) AND TS=(randomized controlled trial OR observational study) NOT TS=(home) NOT TS=(case control) NOT TS=(case report) NOT TS=(review) NOT TS=(child) NOT TS=(newborn)

Cochrane: 162 studies found in 2021, 03.

[(parenteral nutrition):tl,ab,kw] AND [(sepsis):tl,ab,kw OR (infection):tl,ab,kw OR (mortality):tl,ab,kw OR (candidemia):tl,ab,kw OR (bacteremia):tl,ab,kw] AND [(randomized clinical trial):pt OR observational study):pt NOT (case control):pt NOT (case report):pt] AND [(adults):tl,ab,kw NOT (child):tl NOT (newborn):tl NOT (infant):tl NOT (home):tl

Supplementary Table 1: Exclusions

	Year	First author	Title	Reason	Journal
1	1980	Haffejee, A.A.	Nutritional Support in High-Output Fistulas of the Alimentary Tract	Case control	SA Medical Journal
2	1981	Sako, K.	Parenteral hyperalimentation in surgical patients with head and neck cancer: A randomized study	PN without lipids	J Surg Oncol
3	1984	Bauer, E.	Nutrition physiologic, immunologic and clinical parameters in prospective randomized patients by enteral or parenteral nutrition therapy following large intestine operations	German language	Infusionsther Klin Ernahr
4	1987	Herndon, D.N.	Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients.	PN without lipids	J Trauma
5	1987	Szeluga, D.Z.	Nutritional support of bone marrow transplant recipients: a prospective, randomized clinical trial comparing total parenteral nutrition to an enteral feeding program	PN without lipids	Cancer Res
6	1987	Harry C. Sax	Early Total Parenteral Nutrition in Acute Pancreatits: Lack of Beneficial Effects	Early vs late PN	The American Journal of Surgery
7	1989	Ebener	The effect of preoperative parenteral nutrition on the perioperative course in patients with esophageal cancer	German language	Langenbecks Arch Chir
8	1989	Herndon, D.N.	Increased mortality with intravenous supplemental feeding in severely burned patients	PN without lipids	J Burn Care Rehabil
9	1990	Sitzmann, J.V.	Nutritional Support of the Dysphagic Patient: Methods, Risks, and Complications of Therapy	Incomplete data	Journal of Parenteral and Enteral Nutrition
10	1990	Hamaoui, E.	Enteral Nutrition in the Early Postoperative Period: A New Semi-Elemental Formula Versus Total Parenteral Nutrition	Not reported outcomes	Journal of Parenteral and Enteral Nutrition
11	1993	Iovinelli, G.	Nutrition Support After Total Laryngectomy	Not reported outcomes	Journal of Parenteral and Enteral Nutrition
12	1993	Gonzalez-Huix F.	Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis	Full text not available	American Journal of Gastroenterology
13	1994	Demeyer, I.	Long-term sedation in the ICU: enteral versus parenteral feeding	Full text not available	Clin Intensive Care
14	1995	Braga, M.	Benefits of Early Postoperative Enteral Feeding in Cancer Patients	Duplicate population	Infusionsther Transfusionsmed
15	1995	Schilling, J.	Clinical Outcome and Immunology of Postoperative Arginine, w-3 Fatty Acids and Nucleotide-Enriched Enteral Feeding: A Randomized Prospective Comparison with Standard Enteral and Low Calorie/Low Fat IV Solutions	PN without protein	Nutrition
16	1996	Braga, M.	Immune and nutritional effects of early enteral nutrition after major abdominal operations	Full text not available	European Journal of Surgery
17	1996	Chiarelli	Total enteral nutrition versus mixed enteral and parenteral nutrition in patients at an intensive care unit	Italian language	Minerva Anestesiol
18	1997	Engel, J.M.	Effects of various feeding regimens in multiple trauma patients on septic complications and immune parameters	German language	Anasthesiol Intensivmed Notfallmed Schmerzther
19	1997	Gianotti, L.	Effect of Route of Delivery and Formulation of Postoperative Nutritional Support in Patients Undergoing Major Operations for Malignant Neoplasms	Duplicate population	The Archives of Surgery
20	1998	Braga, M.	Artificial Nutrition After Major Abdominal Surgery: Impact of Route of Administration and Composition of the Diet	Duplicate population	Critical Care Medicine
21	1998	Gianotti	Route and composition of postoperative nutritional support: Impact on immune-metabolic response and postoperative outcome	Italian language	Rivista Italiana di Nutrizione Parenterale ed Enterale
22	2000	Bozzeti, F.	Perioperative Total Parenteral Nutrition in Malnourished, Gastrointestinal Cancer Patients: A Randomized, Clinical Trial	No control group	Journal of Parenteral and Enteral Nutrition
23	2001	Pacelli, F.	Enteral vs Parenteral Nutrition After Major Abdominal Surgery	No control group	The Archives of Surgery
24	2001	Woodcock N.	Enteral Versus Parenteral Nutrition: A Pragmatic Study	Pragmatic study	Nutrition
25	2001	Soliani	Early enteral nutrition in patients treated with major surgery of the abdomen and the pelvis	Italian language	Chir Ital
26	2003	Roberts S.	Total parenteral nutrition vs oral diet in autologous hematopoietic cell transplant recipients	No control group	Bone Marrow Transplantation
27	2004	Chen	Comparative study on the enteral and parenteral nutrition during early postburn stage in burn patients	Mandarin language	Zhonghua Shao Shang Za Zhi
28	2006	Wu	Comparative study of postoperative early enteral nutrition and parenteral nutrition in esophageal carcinoma	Mandarin language	Zhonghua Wei Chang Wai Ke Za Zhi
29	2007	Wu	A randomized controlled trial of postoperative artificial nutrition in malnourished patients with gastrointestinal cancer	Mandarin language	Zhonghua Wei Chang Wai Ke Za Zhi
30	2007	Jiang	Effect of Intravenous glutamine-dipeptide fortified enteral nutrition on clinical outcomes in patients after liver transplantation: A prospective randomized controlled study	Mandarin language	Chinese Journal of Clinical Nutrition

31	2007	Velázquez, J.O.	Soporte nutricional en pacientes con abdomen abierto	Not reported outcomes	Nutrición Hospitalaria
32	2011	Klek, S.	Perioperative nutrition in malnourished surgical cancer patients - A prospective, randomized, controlled clinical trial	Without control group	Clinical Nutrition
33	2013	Sun, J-K.	Effects of early enteral nutrition on immune function of severe acute pancreatitis patients	No intervention	World Journal of Gastroenterology
34	2013	Cui, L.H.	The effects of early enteral nutrition with addition of probiotics on the prognosis of patients suffering from severe acute pancreatitis	Mandarin language	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue
35	2013	Liu, Z.H.	Study on early postoperative nutritional support in elderly patients with gastric cancer	Mandarin language	Zhonghua Wei Chang Wai Ke Za Zhi
36	2013	Roth, B.	Parenteral nutrition does not improve postoperative recovery from radical cystectomy: results of a prospective randomised trial	PN without lipids	Eur Urol
37	2014	Xiao-Bo	Efficacy of early postoperative enteral nutrition in supporting patients after esophagectomy	Full text not available	Minerva Chir
38	2015	Takir, H. B.	Does Total Parenteral Nutrition Increase the Mortality of Patients with Severe Sepsis in the ICU?	Inadequate comparison	Turk Thorac J
39	2015	Tamiya, H.	Comparison of short-term mortality and morbidity between parenteral and enteral nutrition for adults without cancer: a propensity-matched analysis using a national inpatient database	Propensity-score	Am J Clin Nutr

PN: parenteral nutrition

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Supplementary Table 2: Methodology and relevant characteristics of the included trials.

Author, year (country)	Study design	Sample characteristics	Intervention characteristics	Control characteristics	Duration of intervention	Outcomes	Outcome evaluation / Follow up	Glycemic control (hyperglycemia)	Reference (main text)
Lim, 1981 (China)	RCT	Preoperative preparation of patients with carcinoma of the esophagus Age = 64 years (mean) Male = 79.1% Albumin = 3.21 ± 1.05 g/dL (mean ± SD)	TPN (n = 12) - Amoinofusin; Intralipid; Addamel; Soluvit; Vitalipid Protein = 1.56 ± 0.125 g/kg/d Calories = 62.3 ± 3.6 kcal/kg/d	Enteral nutrition by gastrostomy (n = 12) Protein = 2.18 ± 0.187 g/kg Calories = 63.2 ± 7 kcal/kg	4 weeks	Infection, catheter infection, mortality	4 weeks	NA	4
Rapp, 1983 (United States)	RCT	Head injured patients Age = 31.7 ± 3.9 years (mean ± SD) Weight = 58.9 ± 6.8kg Albumin = 3.72 ± 1.75g/dL	TPN (n = 20) – Dextrose + synthetic AA + Soybean oil emulsion Age = 29.2 ± 4.1 years Weight = 58.5 ± 6.7 kg Albumin = 3.72 ± 1.58 g/dL Protein = 1.08 g/kg Calories = 29.9 kcal/kg	Enteral nutrition (n = 18) - Vital Age = 34.9 ± 3.76 years Weight = 59.3 ± 7 kg Albumin = 3.82 ± 1.9 g/dL Protein = 0.42 g/kg Calories = 11.5 kcal/kg	18 days	Length of hospital stay, mortality	1 year	NA	5
Adams, 1986 (United States)	RCT	Trauma patients undergoing an emergent laparotomy	TPN (n = 23) – Isocal or Traumacal Age = 29 ± 10 years (mean ± SD) Male = 69% Weight = 78 ± 19 kg Calories = 36.8 kcal/kg	Enteral (n = 23) – Travasol + Dextrose + Lipid 10% Age = 30 ± 9 years Male = 65% Weight = 74 ± 15 kg Calories = 36.2 kcal/kg	14 days	Length of hospital and ICU stay, pneumonia, abdominal infection, catheter infection, mortality and hyperglicemia	Length of in-hospital stay (31 ± 25 days on average)	Regular insulin if Blood Glucose ≥ 200mg/dL (22% patients days TPN x 10% patients days control)	25
McIntyre, 1986 (England)	RCT	Severe acute colitis	TPN (n = 27) Age = 35.7 years (19 – 56) [median (range)] Male = 48,2%	Oral diet (n = 20) Age = 37.7 years (17 – 72) Male = 30% Albumin = 2.7 g/dL (2.1-4.5) Protein = 80g/dL	7 days	Infection, mortality	Median 43 months (27-64 months)	NA	26

			Albumin = 2.8g/dL (2-3,8) Protein = 77.5g/d Calories = 2200kcal/d	Calories = 1800kcal/d					
Hadley, 1986 (United States)	RCT	Head injured and Glasgow scale of 10 or less Age = 28 years	TPN (n = 24) – Intralipid (Kabivitum) Male = 91.6% Albumin = 3.7 g/dL Craniotomy = 33.3% Protein = 81 ± 28.7 g/d (mean ± SD) Calories = 2070 ± 726 kcal/d	Enteral (n = 21) - Isocal Male = 85.7% Albumin = 3.4 g/dL Craniotomy = 57.1% Protein = 71 ± 40 g/d Calories = 1870 ± 1050 kcal/d	14 days	Infection, pneumonia, mortality	15 weeks	NA	27
Fasth, 1987 (Sweden)	RCT	Postoperative on major colorectal surgery for carcinoma of the large bowel or inflammatory bowel disease	TPN (n = 48) Calories (non-protein) = 45 ± 1.6 kcal/kg/d (mean ± SD) Protein = 1.34 ± 0.05	NPO (n = 44) – 10% dextrose with electrolytes until an oral diet was tolerated Calories = 16 ± 0.8 kcal/kg/d	Minimum of 7 days or until oral diet tolerated (mean 9.7 ± 1.1 days)	Mortality	30 days	NA	28
Young, 1987 (United States)	RCT	Brain-injured patients Glasgow scale of 4-10	TPN (n = 23) Age = 30.3 ± 2.67 years Male = 87% Weight = 72.4 ± 2.6 kg Albumin = 3.1 g/dL Craniotomy = 60.9% Protein = 1.35 ± 0.12 g/kg/d (mean ± SD) Calories at 7^{th} day = 32.5 ± 1.8 kcal/kg/d	Enteral (n = 28) – Traumacal ou Ensure Plus Age = 34 ± 2.92 years Male = 78.5% Weight = 75 ± 3.03 kg Albumin = 3.2 g/dL Craniotomy = 42.9% Protein = 0.91 ± 0.09 g/kg/d Calories at 7^{th} day= 19 ± 1.5 kcal/kg/d	18 days	Infection, pneumonia, mortality	1 year	NA	29
Bellantone, 1987 (Italy)	RCT	Preoperative in patients undergoing to major surgery for gastrointestinal disease	SPN (n = 49) Age = 55 years (mean) Male = 70% 35 kcal/kg/d and 1.25 g/kg/d of protein in adition to oral diet	Oral (n = 51) Oral = 58 years Male = 70.5%	7 days	Infection, mortality	NA	NA	30

Moore, 1989 (United States)	RCT	Patients undergoing to laparotomy for abdominal trauma	TPN (n = 36) – Freamine HBC 6.9% + Trophamine 6% Age = 36 ± 2 years (mean ± SD) Male = 76.6% Calories = 2261 ± 60 kcal/d (non-protein intake on day 5) Protein on day 5 = 96.2 ± 2.5 g/d	Enteral (n = 39) – Vivonex TEN Age = 28 ± 2 years Male = 75.8% Calories = 1847 ± 123 kcal/d (non-protein intake on day 5) Protein on day 5 = 77.5 ± 5 g/d	NA	Infection, pneumonia, abdominal infection, catheter infection, hyperglycemia	NA	Insulin if needed (17% TPN x 3% control)	31
Woolfson, 1989 (England)	RCT	Patients undergoing to major thoraco-abdominal procedures or total cystectomy Nutritional target = 35 kcal/kg/d	TPN (n = 62) – Freamine II + Intralipid 10% Age = 63.3 ± 8,9 years (mean ± SD) Male = 72.5% Weight = 66.2 ± 10.4 kg	NPO (n = 60) – 0.9% saline and 5% dextrose Age = 62 ± 9.2 years Male = 68.3% Weight = 67.1 ± 12.4 kg	6 days	Length of hospital stay, mortality	Length of in-hospital stay	NA	32
Fan, 1989 (China)	RCT	Pre operative in patients undergoing to surgery for oesophageal cancer	SPN (n = 20) - Vamin Age = 64.9 ± 8.9 years (male ± SD) Male = 95% Weight = 46.2 ± 7.03 kg Albumin = 3.9 ± 0.45 g/dL Calories = 55.4 ± 9.7 kcal/kg/d Protein = 2.37 ± 0.26 g/kg	Oral (n= 20) Age = 64.5 ± 9.5 years Male = 90% Weight = 48.9 ± .84 kg Albumin = 4.1 ± 0.45 g/dL Calories = 27.2 ± 10.1 kcal/kg/d Protein = 1.48 ± 0.41 g/kg	14 days	Length of hospital stay, pneumonia, mortality	Length of in-hospital stay (until 185 days)	NA	33
VETERANS, 1991 (United States)	RCT	Malnourished patients undergoing to nonemergency laparotomy or thoracotomy Age = 62.9 ± 9.9 years (mean ± SD) Male = 99%	TPN (n = 231) – Intralipid (Kabivitrum) + Freamine III (Kendal) Calories = 2944 (420 – 4543) kcal/day [mean (range)]	Oral (n = 228) Calories = 1280 (0 – 3342) kcal/day [mean (range)]	10-18 days	Infection, pneumonia, abdominal infection, mortality	30 days	Serum glucose level > 300mg/dl (TPN 16.4% X oral 1.3%)	34

		Weight = 66 ± 13.6 kg Albumin = 3.7 ± 0.36 g/dL							
Kudsk, 1992 (United States)	RCT	Patients with intra-abdominal injury requiring laparotomy Nutritional target = 30-35 kcal/kg/d and 1.5-2 g/kg/d of protein	TPN (n = 46) – Travasol (Clintec) + Intralipid Age = 30.6 ± 1.4 years (mean ± SD) Non-proteic calories = 19.1 ± 3.3 kcal/kg/d	Enteral (n = 52) – Vital HN (Ross) Age = 30.4 ± 1.7 years Non-proteic calories = 15.7 ± 4.2 kcal/kg/d	NA	Length of hospital stay, infection, pneumonia, abdominal infection, catheter infection	15 days	NA	35
Meyenfeldt, 1992 (Netherlands)	RCT	Pre-operative nutrition of patients with gastric or colorectal carcinoma requiring surgical treatment	TPN (n = 51) – Sythamin + dextrose + Intralipid Age = 67.3 ± 10.2 years (mean ± SD) Male = 56.9% Albumin = 3.35 ± 0.38 g/dL Calories = 1783 ± 350 kcal/d Protein = 74.3 ± 15.6 g/d	Enteral (n = 50) – Precitene or Isotein Age = 65.7 ± 9.3 Male = 64% Albumin = 3.55 ± 0.4 g/dL Calories = 1458 ± 444 kcal/d Protein = 128.12 ± 34.3 g/d	10 – 23 days (mean 11.8 days)	Length of hospital stay, pneumonia, abdominal infection, mortality	Length of in-hospital stay (mean 36.3 ± 17.7 days)	NA	36
Sandström, 1993 (Sweden)	RCT	Postoperative of patients undergoing major general surgical procedures	TPN (n = 150) – Intralipid + Vamin Age = 64 ± 4 years (mean ± SD) Male = 62.6% Weight = 70.3 ± 1.1 kg Diabetes = 8% Albumin = 2.79 ± 0.37 g/dL	NPO (n= 150) – 10% dextrose (250-300g) with electrolytes until oral diet tolerated Age = 64 ± 4 years Male = 62.6% Weight = 70 ± 1.2 kg Diabetes = 7.3% Albumin = 2.67 ± 0.12 g/dL	9 ± 1 days	Length of hospital stay, infection, pneumonia, mortality	14 days	NA	37
Borzotta, 1994 (United States)	RCT	Patients with head injuries with Glasgow Coma Scale score of 8 or less and coma persisting over 24 hours	TPN (n = 23) Age = 28.9 ± 10 years Male = 90% APACHE II = 14.9 ± 3.9	Enteral (n = 36) – Isotein HN, Vivonex TEN and 10% Travasol Age = 26.2 ± 10.4 years Male = 75% APACHE II = 15.7 ± 3.5	3.9 ± 3.8 days	Length of hospital stay, pneumonia, abdominal infection, catheter infection, mortality	Length of in-hospital stay (mean 36.9 ± 14 days)	Blood glucose > 180 mg/dL treated with exogenous insulin (76.2% TPN x 44.4% enteral)	38
Brennan, 1994	RCT	Postoperative of	TPN (n = 60)	NPO (n = 57) – saline with	Until oral diet	Length of hospital	Length of in-	NA	39

(United States)		patients undergoing major pancreatic resections Nutritional target = 30-35 non-protein kcal/kg/d and 1 g/kg/d of protein	Age = 65 (34-86) years [median (range)] Male = 56.6% Albumin = 3.1 (1.2-4.8) g/dL	glucose until oral diet tolerated Age = 63 (30-86) Male = 47.3% Albumin = 3.3 (1.8-4.7)	tolerated (12.3 [6-34] days)	stay, infection, pneumonia, abdominal infection, catheter infection, mortality	hospital stay		
Dunham, 1994 (United States)	RCT	Seriously injured and ventilator-dependent blunt trauma patients Nutritional target = 1.75 g/kg/d of protein	TPN (n = 15) + SPN (n = 10) TPN: Calories = 2110 ± 342 kcal/d (mean ± SD) Protein = 133 ± 11 g/d SPN: Calories = 2218 ± 335 kcal/d Protein = 132 ± 23 g/d	Enteral – Traumacal (Mead Johnson) + Naveco + Whey Protein Calories = 1931 ± 353 kcal/d Protein = 120 ± 22 g/d	7 days	Catheter infection, mortality	NA	NA	40
Fan, 1994 (Hong Kong)	RCT	Perioperative of patients undergoing hepatectomy for hepatocellular carcinoma Nutritional target = 30 kcal/kg/d and 1.5 g/kg/d of protein	SPN (n = 64) Age = 54 (28-72) years [median (range)] Male = 87.5% Weight = 57 (51-94)kg Weight loss >10% = 18% Albumin = 4.2 (3.1-5.1) g/dL	Oral (n = 60) – saline with 5% dextrose during immediate postoperative until oral tolerated again Age = 53 (33-79) years Male = 88.3% Weight = 57 (44-82)kg Weight loss >10% = 14% Albumin = 4.2 (2.9-5) g/Dl	14 days (7 days preoperative and 7 days postoperative)	Length of hospital stay, infection, pneumonia, abdominal infection, catheter infection, mortality	Length of in-hospital stay (15 [2-126] days)	Plasma glucose level higher in TPN than oral (2 patients x 0)	41
Wicks, 1994 (England)	RCT	Postoperative of patients undergoing orthotopic liver transplantation Age = 46 years	TPN (n = 10) – Synthamin (Clintec) + Intralipid (Kabi) Male = 50%	Enteral (n = 14) – Osmolite (Abbot) Male = 64.3%	Until oral diet tolerated (4 [4-55] days) (median [range])	Length of hospital stay, infection, mortality	Length of in-hospital stay - 32 ± 29 (mean ± SD) days	NA	42
Sedman, 1995 (England)	Retrospective cohort	Perioperative of patients undergoing elective laparotomy Nutritional target = 35 kcal/kg/d and 1.25	TPN (n = 28) Age = 60.3 ± 3.4 years (mean ± SD) Male = 57.1% Weight loss > 15% = 46%	Oral (n = 175) Age = 64.5 ± 1.2 years Male = 49.1% Weight loss > 15% = 6%	Median 12 (10 – 21) days	Infection, mortality	Length of in-hospital stay	NA	43

		g/kg/d of protein							
Wu, 1995 (Taiwan)	RCT	Postoperative in aged patients (>70 years) with gastric cancer (adenocarcinoma of stomach) Nutritional target = 35 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 31) – China Chemical Age = 74.7 ± 4.8 years (mean ± SD) Male = 100% Weight = 57.9 ± 1.3 kg	Oral (n = 20) Age = 72 ± 1 years Male = 85% Weight = 61 ± 2 kg	10 days	Infection, pneumonia, abdominal infection, fungaemia, mortality	Length of in-hospital stay	NA	44
Hadfield, 1996 (England)	RCT	Critical ill patients with more than 3 days in ICU Age = 54 to 79 years Male = 70.8% Surgical = 87.5%	TPN (n = 11) – Kabi 1 or 5 Age = 64.6 ± 2.6 years (mean ± SD) APACHE II = 13.3 ± 1.2 Surgical = 81.7%	Enteral (n = 13) – Alotraq (Abbot) + Glutamin Age = 66.2 ± 2 years APACHE II = 16.9 ± 1.2 Surgical = 93.2%	NA	Mortality	NA	NA	45
Hernandez-Aranda, 1996 (Mexico)	RCT	Postoperative of patients with severe pancreatitis and need of surgery Nutritional target = 1.92 g/kg/d of protein	TPN (n = 12) Age = 35.5 ± 12.2 years (mean ± SD) Male = 58.3% Albumin = 2.86 ± 0.74 g/dL	Enteral (n = 10) – Vivonex TEN Age = 36 ± 11.7 years Male = 60% Albumin = 2.87 ± 0.56 g/dL	NA	Catheter infection, mortality	NA	NA	46
Baigrie, 1996 (Australia)	RCT	Postoperative of patients undergoing oesophagectomy or gastrectomy	TPN (n = 47) Male = 59.5% Malnourished = 36.2%	Enteral (n = 50) – Osmolyte HN (Ross) Male = 60% Malnourished = 34%	Until >2000 kcal tolerated per oral	Catheter infection, mortality	NA	NA	47
Reynolds, 1997 (England)	RCT	Postoperative of patients undergoing major upper gastrointestinal surgery for esophageal, gastrc or pancreatic malignancy	TPN (n = 34) – Pharmacia and Upjohn (Milton Keynes) Age = 67 (25-86) years [median (interquartile range)] Male = 79.4% Malnourished = 79.4%	Enteral (n = 33) – Osmolite (Ross) Age = 69 (51-81) years Male = 78.8% Malnourished = 61.1% CRP = 12 (7-17) mg/L Albumin = 3.6 (2.8-4.1) g/dL Calories = 1300 ± 300 kcal/d	7 days	Infection, pneumonia, abdominal infection, catheter infection, mortality	30 days	NA	48

			CRP = 8 (5-28) mg/L Albumin = 3.8 (3.1-4.1) g/dL Calories = 1800 ± 100 kcal/d (mean ± SD) Protein = 62.5 ± 6.25 g/d	Protein = 49.5 ± 18.7 g/d					
Kalfarentzos, 1997 (Greece)	RCT	Patients with acute severe pancreatitis Nutritional target = 30-35 kcal/kg/d and 1.5-2 g/kg/d of protein	TPN (n = 20) – Vamin 18FE, Lipofundin, Dextrose Age = 67.2 ± 8.9 years (mean ± SD) Male = 35% CRP = 335 (140-513) mg/L [mean (range)] APACHE II = 11.8 ± 1.9 Calories = 30.3 kcal/kg/d Protein = 1.45 g/kg/d	Enteral (n = 18) – Reabilan HN Age = 63 ± 10.7 years Male = 44% CRP = 290 (157-427) mg/L APACHE II = 12.7 ± 2.6 Enteral = 29.8 kcal/kg/d Protein = 1.43 g/kg/d	32.8 days (mean)	Length of ICU stay, length of hospital stay, infection, pneumonia, abdominal infection, catheter infection, mortality, hyperglycemia	Length of in-hospital stay (mean 40 days)	Insulin to keep glucose blood level < 200 mg/dL (45% TPN x 22.2% enteral)	6
McClave, 1997 (United States)	RCT	Patients with acute pancreatitis or an acute flare of chronic pancreatitis Nutritional target = 25 kcal/kg/d and 1.2 g/kg/d of protein	TPN (n = 16) Age = 45.1 ± 4.2 years (mean ± SD) Male = 81.2% Albumin = 3.95 ± 0.09 g/dL APACHE III = 22.4 ± 5 Calories = 25 kcal/kg/d Protein = 1.2 g/kg/d Achieved in 81% in 3 days	Enteral (n = 16) Age = 47.6 ±4 years Male = 68.7% Albumin = 3.94 ± 0.18 g/dL APACHE III = 17.5 ± 4.1 Calories = 25 kcal/kg/d Protein = 1.2 g/kg/d Achieved in 72% in 3 days	Mean 7.1 days	Length of ICU stay, length of hospital stay, infection, pneumonia, catheter infection, mortality	Length of in-hospital stay (mean 11.9 days)	Need for insulin or oral hypoglycemic agent	49
Windsor, 1998 (United Kingdom)	RCT	Acute pancreatitis	TPN (n = 18) – Kabi Regimen 1 (Pharmacia and Upjohn) Age = 63 (52-73) years [median (interquartile range)] Male = 43.7% CRP = 4.5 (2.5-5.5) mg/L	Enteral (n = 16) – Osmolite, Entera, Fortisip Age = 62 (47 – 76) years Male = 38.8% CRP = 3 (2.5 – 5) mg/L Albumin = 3.8 (3.8 – 4.1) mg/dL APACHE II = 8 (6 – 10) Calories = 1430 (925 – 1715) kcal/d	7 days	Length of hospital stay, infection, mortality	30 days	NA	50

			Albumin = 3.55 (3-3.65) mg/dL APACHE II = 9.5 (8-13) Calories = 2166 kcal/d Protein = 58.7g/d	Protein = 57.7 g/d					
Hu, 1998 (United States)	RCT	Postoperative of patients undergoing staged spinal reconstructive procedures	TPN (n = 19) Age = 54 (3-75) [mean [range]) years Male = 25%	NPO (n = 21) Age = 47 (20-73) years Male = 20%	Until >50% prescribed oral diet tolerated	Infection	Length of in-hospital stay (mean 18.1 days)	NA	51
Di Carlo, 1999 (Italy)	RCT	Postoperative of patients undergoing pancreaticoduodenectomy for adenocarcinoma of the pancreatic head Nutritional target = 25 kcal/kg/d	TPN (n = 32) Age = 62.4 ± 11.3 years (mean ± SD) Male = 59% Malnourished = 37.5% Albumin = 3.72 ± 0.42 g/dL Calories = 1710 ± 370 kcal/d	Enteral (n = 68) – standard or immunonutrition (Impact, Novartis) Age = 62.3 ± 12.55 years Male = 63% Malnourished = 39.7% Albumin = 3.78 ± 0.42 g/dL Calories = 1565 ± 340 kcal/d	Until > 800 kcal/day tolerated per oral (mean 12.2 ± 4.6 days)	Length of hospital stay, infection, pneumonia, abdominal infection, mortality	Length of in-hospital stay (mean 19.3 ± 8 days)	NA	52
Bauer, 2000 (France)	RCT	Patients admitted to ICU for more than 2 days and expected to eat less than 20 kcal/kg/d for more than 2 days Nutritional target = 25 kcal/kg/d	SPN (n = 60) – Vitrimix KV / Soluvit Age = 53 ± 18 years (mean ± SD) Male = 66% Weight = 75 ± 16 kg IMC = 26 ± 5 kg/m² Malnourished = 40% CRP = 161.3 ± 99.3 mg/L Albumin = 2.24 ± 0.61 g/dL SAPS II = 43 ± 14 Surgical = 41.6% Calories = 24.6 ± 4.9 kcal/kg/d	Enteral (n = 60) Age = 55 ± 18 years Male = 70% Weight = 75 ± 15 kg BMI = 26 ± 5 kg/m² Malnourished = 41.6% CRP = 161 ± 81.8 mg/L Albumin = 2.17 ± 0.72 g/dL SAPS II = 41 ± 13 Surgical = 56.6% Calories = 14.2 ± 6.5 kcal/kg/d	4 – 7 days	Length of ICU stay, length of hospital stay, pneumonia, mortality	90 days and 2 years	Insulin sliding scale to keep blood glucose 160 – 200mg/dL	53
Bozzeti, 2001 (Italy)	RCT	Postoperative of patients with weight loss greater than 10%,	TPN (n = 158) Age = 64.1 ± 9.8 years (mean ± SD) Male = 58.2%	Enteral (n = 159) Age = 64.8 ± 10.8 years Male = 58.5% Diabetes = 11% Albumin = 3 ± 0.5 g/dL	9.6 ± 4.3 days (until oral diet tolerated)	Length of ICU stay, length of hospital stay, infection, pneumoni	Length of in-hospital stay (10.4 ± 4.5 days)	NA	54

		cancer and major planned elective surgery Nutritional target = 27 kcal/kg/d and 1.4 g/kg/d of protein	Diabetes = 11% Albumin = 3.5 ± 0.5 g/dL Calories = 1750 kcal/d (average energy intake in the first 7 days) Protein = 1.4 g/kg/d	Calories = 1650 kcal/d (average energy intake in the first 7 days) Protein = 1.4 g/kg/d		a, mortality			
Braga, 2001 (Italy)	RCT	Postoperative of cancer of stomach, pancreas or esophagus Nutritional target = 25 kcal/kg/d	TPN (n = 131) Age = 62.9 ± 12.4 years (mean ± SD) Male = 54.1% Weight = 66.8 ± 14.9 kg Malnourished = 36.6% Albumin = 3.7 ± 0.4 g/dL Calories = 24.4 ± 4.2 kcal/kg	Enteral (n = 126) Age = 64.1 ± 13.1 years Male = 53.9% Weight = 65.9 ± 13.7 kg Malnourished = 34.1% Albumin = 3.7 ± 0.4 g/dL Calories = 23.09 ± 4.73 kcal/kg	13.2 ± 4.9 days (until oral diet tolerated)	Length of hospital stay, infection, pneumonia, abdominal infection, mortality	Length of in-hospital stay (22.6 ± 9.7 days)	Glucose serum concentration greater than 200mg/dL for two consecutive measurements (9.1% PN x 4.7% enteral)	55
Abou-Assi, 2002 (United States)	RCT	Acute pancreatitis Nutritional target = 25-30 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 27) Age = 50 ± 3 years (mean ± SD) Male = 48.1% BMI = 25.7 ± 1.6 kg/m²	Enteral (n = 26) Age = 48 ± 3 years Male = 61.5% BMI = 26.6 ± 1.3 kg/m²	10.8 ± 1.7 days (until oral diet tolerated)	Length of hospital stay, catheter infection, mortality, hyperglycemia	Length of in-hospital stay (18.4 ± 1.9 days)	Required insulin therapy (on a sliding scale); 51.8% PN x 15.3% enteral	56
Oláh, 2002 (Hungary)	RCT	Acute pancreatitis Nutritional target = 30 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 48) – Rindex 10, Infusamin S, Intralipid Age = 43.8 years (mean) Male = 87.5%	Enteral (n = 41) – Survimed OPD Age = 47.2 years Male = 87.8%	5-16 days (min-max)	Infection, mortality	NA	NA	57
Aiko, 2003 (Japan)	RCT	Patients with esophageal carcinoma undergoing curative surgical intervention	TPN (n = 19) – Dextrose + Intralipos 10% (Welfide) + Aminotripa Age = 68.2 ± 2 years (mean ± SD) Male = 89.7% Weight = 55.8 ± 2 kg	Enteral (n = 20) – Ensure Liquid (Dainabot) Age = 61 ± 3 years Male = 80% Weight = 55.1 ± 3.3 kg	At least 7 days	Infection, pneumonia, mortality	30 days	NA	58

Bertolini, 2003 (Italy)	RCT	Critical ill patients, judged to need artificial ventilation and nutrition for at least 4 days Nutritional target = 25-28 kcal/kg/d	TPN (n = 21) Age = 59 ± 21.4 years (mean ± SD) Male = 47.6% SAPS II = 41 (35-51) [median (IIQ)] Surgical = 28.5% Calories = 25.9 ± 6.4 kcal/kg	Enteral (n = 18) – Perative (Abbot) Age = 59.3 ± 21.4 years Male = 61.1% SAPS II = 41 (39-46) Surgical = 16.6% Calories = 19.1 ± 7.6 kcal/kg	At least 6 days	Length of ICU stay, mortality	28 days	NA	59
Gupta, 2003 (United Kingdom)	RCT	Severe Acute Pancreatitis Nutritional target = 36 kcal/kg/d	TPN (n = 10) – Dextrose + lipid 10% + Synthamin Age = 57 (38-86); [median (range)] Male = 33.3% CRP = 161 (16-290) mg/L APACHE II = 10 (7-14)	Enteral (n = 11) – Nutrison and Polycal (Nutrica) Age = 65 (56-89) Male = 50% CRP = 54 (15-254) mg/L APACHE II = 8 (6-12)	4 (2-7) days	Length of hospital stay, infection, pneumonia, catheter infection, mortality	Length of in-hospital stay (10 days in median)	NA	60
Xian-Li, 2004 (China)	RCT	Severe Acute Pancreatitis Nutritional target = 25 kcal/kg/d and 1.25 g/kg/d of protein	TPN (n = 41) Age = 39.8 ± 8.2 years (mean ± SD) Male = 53.6% Weight = 70.65 ± 14.5 kg Albumin = 2.9 ± 0.46 g/dL Calories = 25 kcal/kg Protein = 1.25 g/kg/d	NPO (n = 23) Age = 39.6 ± 5.2 years Male = 52.1% Weight = 67.5 ± 14.37 kg Albumin = 2.87 ± 0.49 g/dL	At least 14 days	Length of hospital stay, abdominal infection, mortality	Length of in-hospital stay (mean 31 days)	NA	61
Louie, 2005 (Canada)	RCT	Severe Acute Pancreatitis Nutritional target = 25 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 18) – Intralipid (Baxter) Age = 59 ± 15.3 years (mean ± SD) Male = 50% Weight = 84.4 ± 15.3 kg BMI = 28.6 ± 3.7 kg/m² NPO time = 4.1 ± 2.5 days Albumin = 3.39 ± 0.74 g/dL	Enteral (n = 10) – Peptamen (Nestle) Age = 65.3 ± 18.3 years Male = 60% Weight = 823 ± 14.8 kg BMI = 28.2 ± 3.8 kg/m² NPO time = 3.5 ± 1.1 days Albumin = 3.34 ± 0.79 g/dL APACHE II = 11.8 ± 8.3 Calories = 18.2 ±5.9 kcal/kg/d	14.6 ± 10.3 days	Abdominal infection, catheter infection, mortality, hyperglycemia	NA	Blood glucose level higher than 198 mg/dL on 2 consecutive readings were deemed to have a day of elevated blood glucose. (TPN: 3.6 days x enteral:	62

			APACHE II = 12.7 ± 5.5 Calories = 21.4 ± 3.9 kcal/kg/d					2.7 days). Both groups received insulin sliding scale to reach glucose level between 110-180mg/dL	
Zhang, 2005 (China)	RCT	Nutritional support in patients with cirrhotic portal hypertension after pericadial devascularization Age = 41.7 ± 14.9 years (mean ± SD) Male = 72.5% Nutritional target = 25-30 kcal/kg/d and 0.9-1.25 g/kg/d of protein	TPN (n = 20) Albumin = 3.24 ± 0.41 g/dL Calories = 2038 ± 101 kcal/d Protein = 73.1 ± 4.37 g/d	Enteral (n = 20) – Vivonex (Novartis) Albumin = 3.2 ± 0.4 g/dL Calories = 2013 ± 90 kcal/d Protein = 71.8 ± 1.88 g/d	9 days	Length of ICU stay, length of hospital stay, infection, abdominal infection, mortality	Lengh of in-hospital stay (19.2 ± 2.4 days in average)	NA	63
Ávila, 2006 (Mexico)	Retrospective cohort	Patients having radical cystectomy and ileal duct	TPN (n = 81) Age = 62.3 ± 11.3 years (mean ± SD) Male = 72.8%² BMI = 26.3 ± 4.9 kg/m² Diabetes = 16% Malnourished = 46.9% Obesity = 46.9% Albumin = 3.4 ± 0.7 g/dL Calories = 27.8 ± 3.6 kcal/kg/d Protein = 1.4 ± 0.2 g/kg/d	NPO (n = 33) - saline with glucose until oral diet tolerated Age = 62.4 ± 11.9 years Male = 66.6% BMI = 26.9 ± 4.3 kg/m² Diabetes = 21.2% Malnourished = 36.3% Obesity = 48.4% Albumin = 3.9 ± 0.6 g/dL	9.2 ±7.3 days	Length of hospital stay, abdominal infection, catheter infection, mortality	Length of in-hospital stay (20.9 ± 12.1 days)	NA	64
Petrov, 2006 (Russia)	RCT	Severe Acute Pancreatitis	TPN (n = 35) Age = 52 (41-70) [median	Enteral (n = 35) – Peptamen (Nestle) Age = 51 (42-67) years	At least 7 days	Pneumonia, abdominal infection, catheter infection,	Length of in-hospital stay	Insulin requirement (TPN = 14.2% x	65

		Nutritional target = 30 kcal/kg/d and 1.5 g/kg/d of protein	[interquartile range)] Male = 70.5% CRP = 210 (177-246) mg/dL APACHE II = 12.5 (11-16)	Male = 77% CRP = 195 (164-216) mg/dL APACHE II = 12 (10-14)		mortality, hyperglycemia		Enteral = 2.9%)	
Radrizzani, 2006 (Italy)	RCT	Critical ill patients without severe sepsis Nutritional target = 25-28 kcal/kg/d	TPN (n = 147) Age = 49.2 ± 26 years (mean ± SD) Male = 77.2% Malnutrition = 3.4% SAPS II = 37 (26-45) [median (interquartile range)] Surgical = 20.6% Calories = 23.7 ± 8.6 kcal/kg	Enteral (n = 143) - Perative Age = 51.5 ± 22.9 years Male = 71.1% Malnutrition = 3.5% SAPS II = 35.5 (27 – 45) Surgical = 21.1% Enteral = 20 ± 8.3 kcal/kg	At least 6 days	Length of ICU stay, length of hospital stay, infection, pneumonia, abdominal infection, mortality	28 days	Glicemic control to keep blood glucose < 180mg/dL	66
Modena, 2006 (Peru)	Prospective cohort	Severe Acute Pancreatitis with necrosis	TPN (n = 43) Age = 58 ± 14.3 years (mean ± SD) Male = 55.8% CRP = 228 ± 125 mg/L APACHE II = 16 (4 – 26) [mean (range)]	Enteral (n = 44) – Osmolyte HN and Survimed Age = 51 ± 17.7 years Male = 63.6% CRP = 203 ± 150 mg/L APACHE II = 13 (3 – 25)	NA	Abdominal infection, mortality	Length of in-hospital stay	NA	67
Casas, 2007 (Spain)	RCT	Severe Acute Pancreatitis Nutritional target = 30-35 kcal/kg/d and 1.5-2 g/kg/d of protein	TPN (n = 11) Age = 55.6 ± 15.6 years (mean ± SD) Male = 72.7% Day 5: Protein = 1.16 ± 0.05 g/kg/d Calories = 20.8 ± 1.68 kcal/kg/d	Enteral (n = 11) – Peptisorb (Nutricia) Age = 61.2 ± 16.6 years Male =72.7% Day 5: Protein = 0.92 ± 0.1 g/kg/d Calories = 20.09 ± 1.83 kcal/kg/d	At least 10 days	Length of hospital stay, infection, abdominal infection, catheter infection, mortality	Length of in-hospital stay (median 30.5 days)	NA	68
Ryan, 2007 (Ireland)	Retrospective Cohort	Postoperative of total gastrectomy for malignancy Age = 65 ± 12 years (mean ± SD) Male = 64.4%	TPN (n = 38) Weight = 66 ± 15.8 kg BMI = 23.8 ± 4.7 kg/m² Time without nutrition = 0.8 ± 1.5 days	NPO (n = 52) Weight = 76.4 ± 15.7 kg BMI = 26 ± 5.2 kg/m² Time without nutrition = 9.2 ± 3 days	9 days	Length of hospital stay, infection, pneumonia, mortality	3 months	NA	69

		Albumin = 3.7 ± 0.37 g/dL							
Elke, 2008 (Germany)	Prospective Cohort	Critical patients with severe sepsis or septic shock Age = 63 (53-74) years [median (interquartile range)] Male = 58.4% BMI = 26 (23-29) kg/m² APACHE II = 19 (13 – 24)	TPN (n = 140) + SPN (n = 138) TPN: Age = 69 (57-74) years Male = 57.1% BMI = 26 (22 – 29) kg/m² APACHE II = 21 (16 – 26) Surgical = 35.7% SPN: Age = 62 (50 – 73) years Male = 58.7% BMI = 26 (23 – 29) kg/m² APACHE II =19 (13 – 23) Surgical = 38.4%	Enteral (n = 70) + NPO (n = 41) Enteral: Age = 71 (54 – 76) years Male = 58.8% BMI = 26 (23 – 31) kg/m² APACHE II = 17 (12-23) Surgical = 33.8% NPO: Age = 71 (60 – 78) years Male = 61% BMI = 26 (22 – 30) kg/m² APACHE II = 21 (15 – 30) Surgical = 36.6%2008	NA	Length of ICU stay, length of hospitalar stay, mortality	3 months	To keep mean glucose level 180mg/dL (higher insulin need in mixed group)	70
Lam, 2008 (Viet Nam)	RCT	Severe burned patients	TPN (n = 41) – B/Braun Age = 33.3 ± 1.9 years (mean ± SD) Protein = 162 ± 7.8 g/d Calories = 3240.7 ± 32.3 kcal/d	Enteral (n = 41) – Vivonex/Ensure Age = 32 ± 1.5 years Protein = 101 ± 4.6 g/d Calories = 2816.3 ± 42.6 kcal/d	At least 7 days	Pneumonia, mortality	Length of in-hospital stay	NA	71
Doley, 2009 (India)	RCT	Severe acute pancreatitis Nutritional target = 2500-2700 kcal /d and 120-130 g/d of protein	TPN (n = 25) – Claris (Ahmedabad) Age = 41 ± 11.3 years (mean ± SD) CRP = 117.5 ± 118.7 Albumin = 3.1 ± 0.59 g/dL	Enteral (n = 25) Age = 38.4 ± 13.8 years CRP = 162.3 ± 195.4 Albumin = 2.82 ± 0.51	14 days	Length of ICU stay, length of hospital stay, infection, fungemia, mortality	14 days	NA	72
Ryu, 2009 (South Korea)	RCT	Postoperative of untreated laryngeal or pharyngeal (oro or hypopharyngeal)	TPN (n = 40) Age = 62.5 ± 9.1 years (mean ± SD) Male = 92.5 %	Enteral (n = 44) Age = 64.7 ± 8.3 years Male = 85.3%	15 days	Length of hospital stay, infection, pneumonia, catheter infection	6 weeks	Transient elevation of blood glucose level was	73

		squamous cell carcinoma Nutritional target = 25 kcal/kg/d and 0.8-1 g/kg/d of protein						corrected through regular insulin sliding	
Matsushima, 2010 (United States)	Prospective cohort	Critical care patients Nutritional target = 25-35 kcal/kg/d and 1.5-2 g/kg/d of protein	TPN (n = 13) + SPN (n = 22) Age = 50.7 ± 17.2 years (mean ± SD) Male = 65.7% Calories = 1772.6 ± 301 kcal/d	Enteral (n = 120) Age = 47.7 ± 18.3 years (mean ± SD) Male = 67.5% Calories = 1567.1 ± 281.9 kcal/d	NA	Infection, pneumonia, catheter infection,	Length of hospital stay	Tight glucose controle (insulin infusion to achieve glucose level between 80 – 110 mg/dL): TPN 71.4 % x Enteral 49.2	74
Wu, 2010 (China)	RCT	Severe acute pancreatitis Nutritional target = 25-30 kcal/kg/d and 1.2-1.5 g/kg/d of protein	TPN (n = 54) Age = 54 ± 11.2 years (mean ± SD) Male = 55.5% CRP = 218 ± 7.9 mg/dL APACHE II = 16 ± 4.4	Enteral (n = 53) Age = 52 ± 12.1 Male = 60% CRP = 211 ± 9.2 mg/dL APACHE II = 14 ± 2.1	NA	Abdominal infection, mortality	NA	NA	75
Altintas, 2011 (Turkey)	RCT	Critical care patients who needed mechanical ventilation Nutritional target = 25-30 kcal/kg/d and 1.2-1.5 g/kg/d of protein	TPN (n = 41) Age = 57.9 ± 18 years (mean ± SD) Male = 56.1 % BMI = 23.3 ± 4.1 kg/m² APACHE II = 22.6 ± 7.4	Enteral (n = 30) Age = 57.7 ± 19.8 years Male = 50% BMI = 24.3 ± 4.3 kg/m² APACHE II = 20.03 ± 7.43		Length of ICU stay, length of hospital stay, infection, pneumonia, catheter infection, mortality		Continue infusion of insulin if glucose blood level higher than 140mg/dL	76
Arbeloa, 2011 (Spain)	Retrospective cohort	Critical care patients Age = 64 ± 16.8 years (mean ± SD) Nutritional target = 1886 ± 276 kcal/d and 90.6 ± 28.10 g /d of protein	TPN (n = 41) + SPN (n = 19) TPN: APACHE II = 18 ± 7.9 Surgical = 81.6% Calories = 1244.76 ± 63 kcal/d SPN: APACHE II = 19.8 ± 6.3 Surgical = 61.1% Calories = 1621.9 ± 71.7 kcal/d	Enteral (n = 42) APACHE II = 18.8 ± 8.7 Surgical = 20.5% Calories = 697.8 ± 49.6	NA	Length of ICU stay, pneumonia,	Length of ICU stay (19.06 ± 16.9 days)	NA	77

Davies, 2011 (Australia and New Zealand)	Prospective cohort	Acute Pancreatitis in ICU Energy prescribed = 2005 ± 408 kcal (mean ± SD)	TPN (n = 18) Age = 53.5 ± 4 years (mean ± SD) Male = 50% BMI = 29 ± 1.7 kg/m² Diabetes = 28% CRP = 228 ± 34.6 mg/L APACHE II = 17 ± 2	Enteral (n = 27) Age = 54 ± 4 years Male = 44% BMI = 28.6 ± 1.1 kg/m² CRP = 204 ± 30.1 mg/L APACHE II = 16 ± 1.35	4.5 days (2 – 8) [median (interquartile range)]	Mortality	Length of in-hospital stay	NA	78
Justo Meirelles, 2011 (Brazil)	RCT	Traumatic brain injury (Glasgow Coma Scale 9-12) Nutritional target = 25-30 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 10) Age = 31 ± 10 years (mean ± SD) Male = 90% Weight = 73.9 ± 7.2 kg CRP = 61.2 ± 32.2 mg/dL Albumin = 3.2 ± 0.4 g/dL APACHE II = 13 (7-21) [mean (range)]	Enteral (n = 12) Age = 31 ± 13 years Male = 91.6% Weight = 74.9 ± 8.4 kg CRP = 62 ± 47.4 mg/dL Albumin = 3.4 ± 0.5 g/dL APACHE II = 14 (8-22)	5 days	Length of ICU stay, infection, pneumonia, mortality	NA	Higher mean glucose level in TPN (134mg/dL) than enteral (102mg/dL)	79
Aydogmus, 2012 (Turkey)	RCT	Critical care patients Nutritional target = 25-30 kcal/kg/d	TPN (n = 40) Age = 40.6 ± 17.2 years (mean ± SD) Male = 47.5% APACHE II = 21.1 ± 5.9	Enteral (n = 20) Age = 35.5 ± 14.1 years Male =55% APACHE II = 20.7 ± 4.7	5 days	Pneumonia	7 days	NA	80
Elke, 2013 (Germany)	Retrospective cohort	Critical care patients with severe sepsis or septic shock	TPN (n = 25) + SPN (n = 242) TPN: Age = 61 (50-64) years [median (interquartile range)] Male = 68% Weight = 25 (22-29) kg Diabetes = 8% APACHE II = 16 (12-18) Surgical = 52% Protein = 0.55 (0.16-0.9) g/kg/d Calories = 15.6 (10.6-21.4) kcal/kg/d	Enteral (n = 86) Age = 69 (57 – 76) years Male = 65% Weight = 25 (22 – 29) kg Diabetes = 8% APACHE II = 20 (17-24) Surgical = 50% Protein = 0.43 (0.29-0.64) g/kg/d Calories = 11.8 (8.1-17.6) kcal/kg/d	8 (6 – 16) days	Length of ICU stay, infection, mortality	90 days	Trend to higher mean insulin dose/day for TPN and SPN than enteral	81

			SPN: Age = 66 (56-73) years Male = 60.3% BMI = 26 (24-30) kg/m² Diabetes = 24.4% APACHE II = 20 (16 – 24) Surgical = 54.1% Protein = 0.65 (0.37-0.96) g/kg/d Calories = 17.5 (12.9-22.7) kcal/kg/d						
Wang, 2013 (China)	RCT	Severe acute pancreatitis in ICU Nutritional target = 30-35 kcal/kg/d and 2 g/kg/d of protein	TPN (n = 60) Age = 41.7 ± 11.4 years (mean ± SD) Male = 56.6% APACHE II = 14.6 ± 3.6	Enteral (n = 123) – Peptisorb (Nutricia) Age = 43.1 ± 13.7 years Male = 52% APACHE II = 13.1 ± 3	NA	Abdominal infection, mortality	14 days	NA	82
Bito, 2013 (Japan)	Prospective cohort	Hospitalized patients older than 60 years who received artificial nutrition	TPN (n = 146) Male = 54%	Enteral (n = 364) Male = 48.8%	NA	Infection, mortality	1 year	NA	83
Harvey, 2014 (United Kingdom)	RCT	Critical ill patients who were expected to receive artificial nutrition for at least 48 hours Nutritional target = 25 kcal/kg/d	TPN (n = 1200) Age = 63.3 ± 15.1 years (mean ± SD) Male = 57.9% BMI = 27.7 ± 7.4 kg/m² Malnutrition = 12.7% APACHE II = 19.6 ± 6.9 Surgical = 13.6% Calories = 21.3 ± 7.7 kcal/kg/d Protein = 0.7 ± 0.3 g/kg/d	Enteral (n = 1200) Age = 62.9 ±15.4 years Male = 60.6% BMI = 28.2 ±7.5 kg/m² Malnutrition = 12.7% APACHE II = 19.6 ± 6.9 Surgical = 14% Calories = 18.5 ± 7.7 kcal/kg/d Protein = 0.6 ± 0.3 g/kg/d	At least 5 days	Length of ICU stay, length of hospital stay, pneumonia, catheter infection, mortality	1 year	Insulin for blood glucose level higher than 180mg/dL (TPN: 58.6% and Enteral: 56.1%)	7
Reignier, 2015 (France)	Prospective cohort	Mechanically ventilated patients with shock	TPN (n = 481) Age = 66.9 (56.7 – 76.7) years [median	Enteral (n = 1380) Age = 67.2 (54.3 -76.3) years Male = 62.6%	NA	Length of ICU stay, mortality	28 days	NA	84

			(interquartile range)] Male = 65.5% Weight = 70 (60 – 80) kg BMI = 24.3 (21.3 – 27.7) kg/m² Diabetes = 12.5% Obesity = 12.3% Surgical = 48.6% SAPS II = 46 (35-60)	Weight = 70 (60 – 79) kg BMI = 24.3 (21.3-27.3) kg/m² Diabetes = 15% Obesity = 15.4% Surgical = 11.3% SAPS II = 51 (40-64)					
Takesue, 2015 (Japan)	RCT	Patients submitted to thoracoscopic esophagectomy for esophageal cancer	TPN (n = 24) Age = 60.7 ± 8.97 years (mean ± SD) Male = 78.2% Weight = 57.2 ± 12.1 kg Diabetes = 4.3% CRP = 0.13 ± 0.26 mg/dL Albumin = 4.1 ± 0.2 g/dL Calories = 19.3 ± 3.5 kcal/kg	Enteral (n = 25) Age = 63.6 ± 7.13 years Male = 79% Weight = 62.3 ± 11.3 kg Diabetes = 16.7% CRP = 0.09 ± 0.14 mg/dL Albumin = 4 ± 0.4 g/dL Calories = 17.6 ± 2.5 kcal/kg	10 days	Length of ICU stay, length of hospital stay, pneumonia, catheter infection, mortality	14 days	Blood sugar levels were measured four times a day in all patients, and insulin was injected or mixed into infusion solutions, depending on these levels. No differences between groups.	85
Fan, 2016 (China)	RCT	Severe traumatic brain injury (Glasgow Coma Scale 6-8) Nutritional target = 25-30 kcal/kg/d	TPN (n = 40) + SPN (n = 40) Age = 41.95 ± 14.65 years (mean ± SD) Male = 54.7% Weight = 65.05 ± 17.3 kg Albumin = 2.79 ± 0.64 g/dL	Enteral (n = 40) – Nutrison (Nutricia) Age = 40.1 ± 11.2 years Male = 45% Weight = 67.2 ± 21.4 kg Albumin = 2.89 ± 0.63 g/dL	20 days	Length of ICU stay, mortality	NA	NA	86
Gavri, 2016 (Greece)	Prospective cohort	Critical ill patients expected to remain more than 96h in ICU	TPN (n = 43) + SPN (n = 160) TPN: Age = 61 (45-76) years [median (IQR)] Male = 65% CRP = 17 (5.2-29) mg/dL	Enteral (n = 46) Age = 57 (40 – 71) years Male = 63% CRP = 7.7 (3.4 – 17.4) mg/dL Albumin = 3.1 (2.7 – 3.7) g/dL APACHE II = 17 (11 – 21) Surgical = 19.6%	NA	Length of ICU stay, mortality	20 days	Maximum daily glucose higher in SPN than enteral (SPN: 185mg/dL; enteral: 149mg/dL)	87

			Albumin = 2.3 (2-2.8 g/dL APACHE II = 14 (10 – 20) Surgical = 60.5% Calories = 1077 (297-2087) kcal/d Protein = 56 (25-109) g/d SPN: Age = 62 (48 – 73) years Male = 68.1% CRP = 8.9 (3.5 – 17) mg/dL Albumin = 2.9 (2.5 – 3.2) g/dL APACHE = 16 (13 – 21) Surgical = 41.9% Calories = 1291 (890-1891) kcal/d Protein = 74 (46 – 103) g/d	Calories = 415 (157-687) kcal/kg Protein = 22 (10 – 34) g/d					
Perinel, 2016 (France)	RCT	Postoperative of patients undergoing open pancreaticoduodenectomy Nutritional target = 30 kcal/kg/d and 1.5 g/kg/d of protein	TPN (n = 106) Age = 64.02 ± 9.9 years (mean ± SD) Male = 60.3% BMI = 23.76 ± 3.44 kg/m² Diabetes = 23% Albumin = 3.71 ± 0.67 g/dL Calories = 26 kcal/kg	Enteral (n = 106) Age = 65.4 ± 11.2 years Male = 62.1% BMI = 24.99 ± 4.17 kg/m² Diabetes = 20.9% Albumin = 3.78 ± 0.66 g/dL Calories = 14.5	14.2 ± 13.9 days	Length of hospital stay, infection, mortality	90 days	NA	88
Zhang, 2016 (China)	RCT	Patients with burn-induced invasive fungal infection Age = 45.34 ± 1.97 years (mean ± SD) Male = 55% Weight = 58.3 ± 5.43 kg	SPN (n = 60) - Albumin = 2.49 ± 0.45 mg/dL	Enteral (n = 60) – Nutrison Fibre (Nutricia Pharmaceutical) + Cubison Arginine Albumin = 2.61 ± 0.45 g/dL	14 days	Infection	14 days	24 units of insulin for all patients	89

		Daily calorie supply was estimated according to the formula: (kcal/d) = 1000 × body surface area (m2) + 25 × burn area (%).							
Theodorakopoulou, 2016	RCT	Effects of enteral versus parenteral nutrition on outcome of mechanically ventilated septic ICU patients Age = 69.6 ± 19.4 years (mean ± SD) APACHE II = 24 ± 5 SOFA 8 ± 3 BMI = 21.5 ± 3.4	TPN (n = 69)	Enteral (n = 77)	NA	Mortality	Length of ICU stay	NA	90
Chen, 2017 (China)	RCT	Pre operative of gastric outlet obstruction Nutritional target = 35 kcal/kg/d	TPN (n = 37) Age = 52.1 ± 13.2 years (mean ± SD) Male = 56.7% BMI = 21.58 ± 3.13 kg/m² Diabetes = 89.2% Albumin = 3.13 ± 0.33 g/dL Calories = 36.9 ± 1.98 kcal/kg	Enteral (n = 31) - Nutrison Age = 48.6 ± 12.5 years Male = 61.7 % BMI = 20.46 ± 2.86 kg/m² Diabetes = 90.3% Albumin = 3.01 ± 0.39 g/dL Calories = 38.56 ± 3.7 kcal/kg	6.73 ± 2.73 days	Length of hospital stay, pneumonia, abdominal infection, mortality	Length of in-hospital stay	NA	91
Yang, 2017 (China)	Retrospective cohort	Patients in ICU submitted to recanalization of acute mesenteric ischaemia Nutritional target = 25	TPN (n = 88) – Omegaven (Fresenius) Age = 46.2 ± 12.9 years (mean ± SD) Male = 54.5% BMI = 21.4 ± 1.3 kg/m² Diabetes = 20.5%	Enteral (n = 95) – Vivonex (Nestle) and Peptisorb (Nutricia) Age = 47.7 ± 12.7 years (mean ± SD) Male = 57.9% BMI = 21.2 ± 1.3 kg/m² Diabetes = 26.1%	34.7 ± 25.7 days	Length of ICU stay, length of hospital stay, pneumonia, abdominal infection, catheter infection, mortality	6 months	NA	92

		kcal/kg/d and 1.2-1.5 g/kg/d of protein	CPR = 89.1 ± 36.1 g/L Albumin = 3.61 ± 0.22 g/dL APACHE II = 22 (18.3 – 24) [median (IQR)] Calories = 1271 ± 359 kcal	CPR = 92.4 ± 35.8 g/L Albumin = 3.6 ± 0.23 APACHE II = 21 (18 – 25) Calories = 1134 ± 412 kcal					
Terzi, 2017 (France)	Retrospective cohort	ICU patients who receveid non invasive ventilation for more than 2 consecutive days	TPN (n = 74) Age = 67.3 (56.4 – 78.8) years [median (IQR)] Male = 63.5% BMI = 25 (22.2 – 30.2) kg/m² SAPS II = 35.5 (26 – 45)	Oral (n = 351) + Enteral (n = 28) + NPO (n = 622) Oral: Age = 71.6 (59.4 – 80.3) years Male = 59.7% BMI = 25.5 (21.8 – 30.5) kg/m² SAPS II = 33 (25 – 42) Enteral: Age = 66.6 (60.9 – 77.3) years Male = 67.9% BMI = 23.4 (19.2 – 26.7) kg/m² SAPS II = 43.5 (34.5 – 50.5) NPO: Age = 70.4 (59.4 – 80.2) years Male = 61.7% BMI = 26 (22.8 – 30.9) kg/m² SAPS II = 37 (30 – 47)	At least 2 days	Pneumonia, catheter infection	28 days	NA	93
Wischmeyer, 2017 (United States)	RCT	Mechanically ventilated adults patients expected to receive artificial nutrition for more than 48h and with a BMI of <25 or >35 kg/m²	SPN (n = 52) - Olimel N9 (Baxter) Age = 55.8 ± 19.8 years (mean ± SD) Male = 40.4% BMI = 33.5 ± 14.9 kg/m² Obesity = 48.1% APACHE II = 20.5 ± 6.4 Surgical = 40.4% Calories = 1844 ± 420 kcal/d Protein = 106 ± 30 g/d	Enteral (n = 73) Age = 55.1 ± 16.2 years Male = 53.4% BMI = 33.2 ± 15 kg/m² Obesity = 47.9% APACHE II = 20.8 ± 7.2 Surgical = 41.1% Calories = 1728 ± 444 kcal/kg Protein = 100 ± 31 g/kg	7 days	Length of ICU stay, length of hospital stay, infection, pneumonia, abdominal infection, catheter infection, fungaemia, mortality	6 months	Yes	94
Pierantozzi, 2017 (Italy)	Prospective cohort	Parenteral nutrition is associated with mortality in critically ill patients'	TPN (n = 31)	Enteral (n = 77)	NA	Mortality, Infection	ICU length of stay	NA	95

Reignier, 2018 (France)	RCT	Mechanically ventilated adults patients concomitantly with vasoactive therapy	TPN (n = 1208) Age = 66 ± 14 years (mean ± SD) Male = 67% Weight = 79.2 ± 20.3 kg BMI = 27.7 ± 6.8 kg/m² Diabetes = 28% CRP = 159.2 ± 130.6 mg/dL Albumin = 2.58 ± 0.68 g/dL SAPS II = 59 ± 19 Calories = 19.6 ± 5.3 kcal/kg/d Protein = 0.8 ± 0.2 g/kg/d	Enteral (n = 1202) Age = 66 ± 14 years (mean ± SD) Male = 67% Weight = 79.4 ± 20.5 kg BMI = 28 ± 7.2 kg/m² Diabetes = 25% CRP = 170.3 ± 138.3 mg/dL Albumin = 2.55 ± 0.7 g/dL SAPS II = 61 ± 20 Calories = 17.8 ± 5.5 kcal/kg/d Protein = 0.7 ± 0.2 g/kg/d	4 (3-6) days	Length of ICU stay, length of hospital stay, infection, pneumonia, catheter infection, mortality, hyperglicemia	90 days	Yes	96
Riddley, 2018 (Australia)	RCT	Critical ill patients receiving mechanical ventilation and expected to continue until the day after randomization with central venous access and one or more organic system failure Nutritional target = 25 kcal/kg/d	SPN (n = 51) – Olimel N9-840 (Triomel) Age = 59 ± 17 years (mean ± SD) Male = 69% BMI = 29 ± 6 kg/m² CRP = 217 ± 111 mg/L APACHE II = 18 ± 7 Surgical = 53% Calories = 24.9 ± 6.4 kcal/kg Protein = 1 ± 0.3 g/kg/d	Enteral (n = 49) Age = 60 ± 17 years Male = 73% BMI = 30 ± 6 kg/m² CRP = 209 ± 97 mg/L APACHE II = 19 ± 7 Surgical = 61% Calories = 16.8 ± 8.2 kcal/kg Protein = 0.6 ± 0.3 g/kg/d	7 days	Length of ICU stay, length of hospital stay, infection, mortality	6 months	Morning blood glucose and daily insulin dose was lower in the enteral group.	97
Wang, 2018 (China)	RCT	Post operative of patients submitted to radical gastrectomy Nutritional target = 25 kcal/kg/d and 1.25 g/kg/d of protein	TPN (n = 63) Age = 48.2 ± 6.1 years (mean ± SD) Male = 50.7%	Enteral (n = 66) Age = 48 ± 7.4 years Male = 51%	NA	Length of hospital stay, pneumonia, catheter infection	NA	Blood glucose fluctuation higher in TPN group	98
Guo, 2019 (China)	Prospective cohort	Severe burns in ICU Weight = 65.8 ± 21.5 kg	SPN (n = 89) Age = 35.2 ± 9.2 years (mean ± SD)	Enteral (n = 11) Age = 37.1 ± 8.1 years Male = 27.3% APACHE II = 9.2 ± 4.7	25 days	Mortality	Length of in-hospital stay	Yes	99

		BMI = 21.6 ± 1.5 kg/m² Nutritional target = 33.8 kcal/kg/d and 2 g/kg/d of protein	Male = 60.5% APACHE II = 12.8 ± 3.1 Calories = 34 ± 6.2 kcal/kg Protein = 1.2 ± 0.6 g/kg/d	Calories = 36.2 ± 7.1 kcal/kg Protein = 1 ± 0.5 g/kg/d					
Berger, 2019 (Switzerland)	RCT	Mechanically ventilated patients with a functional gut, who by end of day 3 did not receive 60% of the equation target (25 kcal/kg*day) by EN alone, and who were expected to require a further 5 days of ICU therapy with full treatment.	SPN (n = 11) Age = 63 (55 – 73) years [Median (Q1 – Q3)] Male = 81.8% Weight = 79 (69 – 98) kg BMI = 27.8 (26.3 – 30.9) kg/m² APACHE II = 25 (17 – 26) SAPS II = 50 (37 – 60) Surgical = 37.5% Calories = 24.3 kcal/kg Protein = 1.11 g/kg/d Glucose = 2.74 g/kg/d	Enteral (n = 12) Age = 67.5 (62.3 – 75) years Male = 83.3% Weight = 77 (75 – 90) kg BMI = 25.2 (23.8 – 29.9) kg/m² APACHE II = 23 (19.2 – 27.8) SAPS II = 45.5 (37.3 – 60) Surgical = 41.6% Calories = 17.8 kcal/kg Protein = 0.69 g/kg/d Glucose = 2.1 g/kg/d	5 days	Length of ICU stay, length of hospital stay, infection, mortality	Length of in-hospital day	Yes, SPN received more insuln than EN (p = 0.0031).	100
Hui, 2019 (China)	RCT	Severe Acute Pancreatitis Age = 51.7 ± 6.3 years (mean ± SD) Male = 51.1% BMI = 20.45 ± 4.39 kg/m² CRP = 72 ± 76 mg/L Albumin = 3.0 ± 0.7 g/dL	TPN (n = 14) + SPN (n = 15) APACHE II = 9.3 ± 0.3 CRP = 32 ± 2 mg/L Albumin = 2.25 ± 1.35 g/dL Calories = 20 – 30 kcal/kg	Enteral (n = 16) APACHE II = 10 ± 0.4 CRP = 36 ± 2.1 mg/L Albumin = 2.1 ± 0.4 g/dL Calories = 20-30 kcal/kg	NA	Mortality, infection	Length of hospital stay	NA	101
Bouleuc, 2020 (France)	RCT	Malnourished patients with advanced cancer and functional gastrointestinal tract. Nutritional target = 30-35 kcal/kg/d	SPN (n = 70) Age = 66.6 ± 9.7 years (mean ± SD) Male = 45.8% BMI = 20.45 ± 4.39 kg/m² CRP = 72 ± 76 mg/L Albumin = 3.0 ± 0.7 g/dL	Oral (n = 78) Age = 66.2 ± 9.2 years Male = 44.4% BMI = 20.68 ± 3.73 kg/m² CRP = 85 ± 72.5 mg/L Albumin = 2.9 ± 0.7 g/dL	NA	Mortality	33.8 months	NA	102

		and 1.2-1.5 g/kg/d of protein							
Groningen, 2020 (Netherlands)	RCT	Adult Hematopoietic Cell Transplantation Recipients Suffering from Gastrointestinal Mucositis Age = 59 (44-69) years ([median (IIQ]) Male = 77.4%	TPN (n = 20)	Enteral (n = 11)	NA	Infection	Length of hospital stay	NA	103

RCT: Randomized Controlled Trial; SD: Standard Deviation; TPN: Total Parenteral Nutrition; NA: not available; SPN: Supplemental Parenteral Nutrition; CRP: C-reactive protein; BMI: Body Mass Index; IQR: interquartile range;

Supplementary Table 3: Comparison regarding severity score, calories and protein received and glycemic control.

Study	Ref	Severity score	Intervention	Control	Similar	Calories received	Intervention	Control	Similar	Protein received	Intervention	Control	Similar	Glycemic control
Lim, 1981 (China)	4	NA				Mean daily energy intake	62.3 ± 3.6 kcal/kg (mean ± SD)	63.2 ± 7 kcal/kg	Yes	Mean daily protein intake	1.56 ± 0.125 g/kg	2.18 ± 0.187 g/kg	No	NA
Rapp, 1983 (United States)	5	Glasgow Coma Scale	7.7 ± 0.56 (mean ± SD)	7.2 ± 0.6	Yes	Mean daily energy intake	29.9 kcal/kg (mean)	11.5 kcal/kg	No	Mean daily protein intake	1.08 g/kg	0.42 g/kg	No	NA
Adams, 1986 (United States)	25	Injury Severity Score	36 ± 12 (mean ± SD)	39 ± 12	Yes	Mean daily energy intake	36.8 kcal/kg	36.2 kcal/kg	Yes	NA				Yes
McIntyre, 1986 (England)	26	NA				Day 7 energy intake	2200 (1400 - 2950) kcal [median (range)]	1800 (1200 – 2700) kcal	Yes	Day 7 protein intake	77.5 (58.1 – 105.6) g	80 (40 – 115) g	Yes	NA
Hadley, 1986 (United States)	27	Glasgow Coma Scale	5.8 (mean)	5.9	Yes	Mean daily energy intake	2070 ± 726 kcal (mean ± SD)	1870 ± 1050 kcal	Yes	Mean daily protein intake	81 ± 28.7 g	71 ± 40 g	No	NA
Fasth, 1987 (Sweden)	28	NA				Mean daily energy intake	45 ± 1.6 kcal/kg (mean ± SD)	16 ± 0.8 kcal/KG	No	Mean daily protein intake	1.34 ± 0.05 g/kg	0	No	NA
Young, 1987 (United States)	29	Glasgow Coma Scale	7 ± 0.31 (mean ± SD)	6.5 ± 0.4	Yes	Day 7 energy intake	32.5 ± 1.8 kcal/kg	19 ± 1.5 kcal/kg	No	Mean daily protein intake	1.35 ± 0.12 g/kg	0.91 ± 0.09 g/kg	No	NA
Bellantone, 1987 (Italy)	30	NA				NA				NA				NA
Moore, 1989 (United States)	31	Revised Trauma Score	6.9 ± 0.3	6.9 ± 0.2	Yes	Day 5 non-protein intake	2261 ± 60 kcal/kg	1847 ± 123 kcal/kg	No	Day 5 protein intake	96.2 ± 2.5 g/d	77.5 ± 5 g/d	No	Yes
Woolfson, 1989 (England)	32	NA				NA				NA				NA
Fan, 1989 (China)	33	NA				Mean daily energy intake	55.4 ± 9.7 kcal/kg	27.2 ± 10.1 kcal/kg	No	Mean daily protein intake	2.37 ± 0.26 g/kg	1.48 ± 0.41 g/kg	No	NA
VETERANS, 1991 (United States)	34	NA				Mean daily energy intake	2944 (420 – 4543) kcal [mean (range)]	1280 kcal	No	NA				Yes
Kudsk, 1992 (United States)	35	Injury severity score	25.1 ± 1.9 (mean ± SD)	25.1 ± 1.7	Yes	Mean non-proteic calories	19.1 ± 3.3 kcal/kg (mean ± SD)	15.7 ± 4.2 kcal/kg	No	NA				NA
Meyenfeldt, 1992 (Netherlands)	36	NA				Mean daily energy intake	1783 ± 350 kcal (mean ± SD)	1458 ± 444 kcal	No	Mean daily protein intake	74.3 ± 15.6 g	128.12 ± 34.3 g	No	NA
Sandström, 1993 (Sweden)	37	NA				NA				NA				NA

Borzotta, 1994 (United States)	38	APACHE II	14.9 ± 3.9 (mean ± SD)	15.7 ± 3.5	Yes	NA				NA				Yes
Brennan, 1994 (United States)	39	NA				NA				NA				NA
Dunham, 1994 (United States)	40	Injury Severity Score	38 ± 12 (mean ± SD) for TPN and 37 ± 15 for SPN	34 ± 18	Yes	Day 7 energy intake	2110 ± 342 kcal (mean ± SD) for TPN e 2218 ± 335 kcal for SPN	1931 ± 353	Yes	Day 7 protein intake	133 ± 11 g for TPN and 132 ± 23 g for SPN	120 ± 22 g	Yes	NA
Fan, 1994 (Hong Kong)	41	NA				NA				NA				Yes
Wicks, 1994 (England)	42	NA				NA				NA				NA
Sedman, 1995 (England)	43	NA				NA				NA				NA
Wu, 1995 (Taiwan)	44	NA				NA				NA				NA
Hadfield, 1996 (England)	45	APACHE II	13.3 ± 1.2 (mean ± SD)	16.9 ± 1.2	Yes	NA				NA				NA
Hernandez-Aranda, 1996 (Mexico)	46	NA				NA				NA				NA
Baigrie, 1996 (Australia)	47	NA				NA				NA				NA
Reynolds, 1997 (England)	48	NA				Mean daily energy intake (first 7 days)	1800 ± 100 kcal (mean ± SD)	1300 ± 300	Yes	Mean daily protein intake (first 7 days)	65.5 ± 6.25g	49.5 ± 18.7g	Yes	NA
Kalfarentzos, 1997 (Greece)	6	APACHE II	11.8 ± 1.9 (mean ± SD)	12.7 ± 2.6	Yes	Mean daily energy intake	30.3 kcal/kg	29.8 kcal/kg	Yes	Mean daily protein intake	1.45 g/kg	1.43 g/kg	Yes	Yes
McClave, 1997 (United States)	49	APACHE III	22.4 ± 5 (mean ± SD)	17.5 ± 4.1	Yes	25kcal/kg/d in 3 days	81%	72%	Yes	1.2 g/kg/d of protein in 3 days	81%	72%	Yes	Yes
Windsor, 1998 (United Kingdom)	50	APACHE II	9.5 (8-13) [median (interquartile range)	8 (6 – 10)	Yes	Mean daily energy intake	2166 kcal	1430 kcal	No	Mean daily protein intake	58.7 g/d	57.7 g/d	Yes	NA
Hu, 1998 (United States)	51	NA				NA				NA				NA

Di Carlo, 1999 (Italy)	52	NA				NA				NA				NA
Bauer, 2000 (France)	53	SAPS II	43 ± 14 (mean ± SD)	41 ± 13 (mean ± SD)	Yes	Mean daily energy intake (first 7 days)	24.6 ± 4.9 kcal/kg	14.2 ± 6.5	No	NA				Yes
Bozzeti, 2001 (Italy)	54	NA				Mean daily energy intake (first 7 days)	1750 kcal	1650 kcal	Yes	Mean daily protein intake (first 7 days)	1.4	1.4	Yes	NA
Braga, 2001 (Italy)	55	Karnofsky Scale Score	76 ± 13 (mean ± SD)	75 ± 12	Yes	Mean daily energy intake	24.4 ± 4.2 kcal	23.09 ± 4.73 kcal	Yes	NA				Yes
Abou-Assi, 2002 (United States)	56	Ranson's Criteria	2.5 ± 0.4 (mean ± SD)	3.1 ± 0.5	Yes	NA				NA				Yes
Oláh, 2002 (Hungary)	57	NA				NA				NA				NA
Aiko, 2003 (Japan)	58	NA				NA				NA				NA
Bertolini, 2003 (Italy)	59	SAPS II	41 (35-51) [median (IIQ)]	41 (39-46)	Yes	Mean for the first 6 days	25.9 ± 6.4 kcal/kg (mean ± SD)	19.1 ± 7.6 kcal/kg	No	NA				NA
Gupta, 2003 (Italy)	60	APACHE II	10 (7-14) [median (range)]	8 (6-12)	Yes	NA				NA				NA
Xian-Li, 2004 (China)	61	NA				Daily	25 kcal/kg	0	No	Daily	1.25 g/kg	0	No	NA
Louie, 2005 (Canada)	62	APACHE II	12.7 ± 5.5 (mean ± SD)	11.8 ± 8.3	Yes	Mean daily energy intake	21.4 ± 3.9 kcal/kg	18.2 ± 5.9 kcal/kg	Yes	NA				Yes
Zhang, 2005 (China)	63	NA				Mean daily energy intake	2038 ± 101 kcal/kg (mean ± SD)	2013 ± 90 kcal/kg	Yes	Mean daily protein intake	73.1 ± 4.37 g/d	71.8 ± 1.88 g/d	Yes	NA
Ávila, 2006 (Mexico)	64	NA				Mean daily energy intake	27.8 ± 3.6 kcal/kg (mean ± SD)	0	No	Mean daily protein intake	1.4 ± 0.2 g/kg	0	No	NA
Petrov, 2006 (Mexico)	65	APACHE II	12.5 (11 - 16) [median (interquartile range)	12 (10 – 14)	Yes	NA				NA				Yes
Radrizzani, 2006 (Italy)	66	SAPS II	37 (26-45) [median (interquartile	35.5 (27 – 45)	Yes	Mean daily energy intake	23.7 ± 8.6 kcal/kg (mean ± SD)	20 ± 8.3 kcal/kg	Yes	NA				Yes

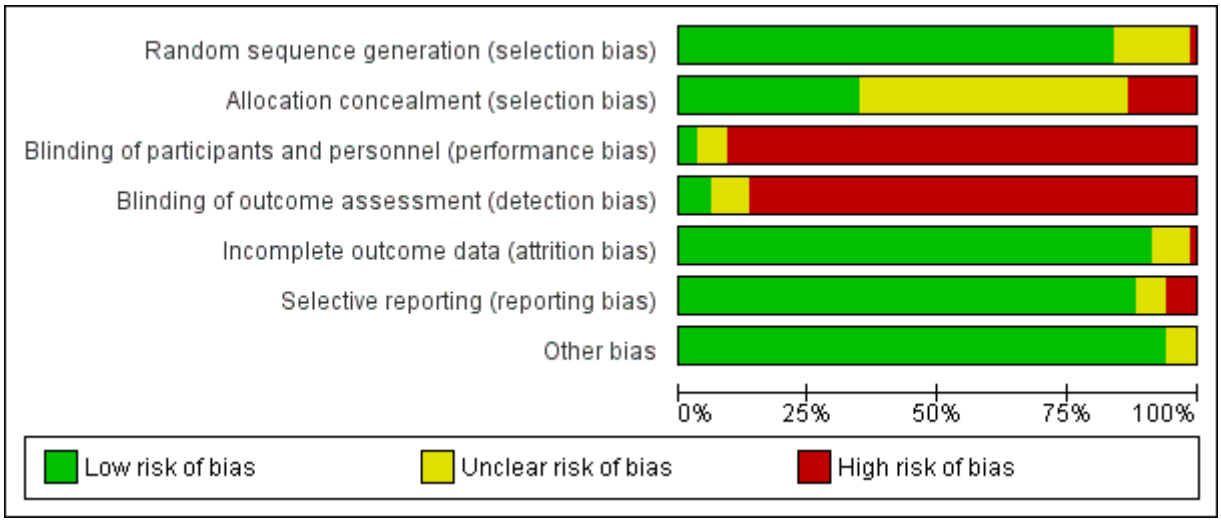
			range)]											
Modena, 2006 (Peru)	67	APACHE II	16 (4 – 26) [mean (range)]	13 (3 – 25)	Yes	NA				NA				NA
Casa, 2007 (Spain)	68	APACHE II	NA	NA	Yes	Day 5 energy intake	20.8 ± 1.68 kcal/kg (mean ± SD)	20.09 ± 1.83 kcal/kg	Yes	Day 5 protein intake	1.16 ± 0.05 g/kg	0.92 ± 0.1	No	NA
Ryan, 2007 (Ireland)	69	NA				NA				NA				NA
Elke, 2008 (Germany)	70	APACHE II	20 (15 – 25) [median (interquartile range)]	18 (13 – 26)	Yes	NA				NA				Yes
Lam, 2008 (Viet Nam)	71	Burn Surface Area	48.6 ± 1.3 years (mean ± SD)	49.8 ± 1.4 %	Yes	Mean of first week energy intake	3240.7 ± 32.3 kcal/d	2816.3 ± 42.6 kcal/d	No	Mean of first week protein Intake	162 ± 7.8 g/d	101 ± 4.6 g/d	No	NA
Doley, 2009 (India)	72	Computed tomography severity index	8.72 ± 1.14 (mean ± SD)	8.84 ± 1.07	Yes	NA				NA				NA
Ryu, 2009 (South Korea)	73	Charlson comorbidity Index	NA	NA	Yes	NA				NA				Yes
Matsushima, 2010 (United States)	74	NA				Mean daily energy intake	1772.6 ± 301 kcal (mean ± SD)	1567.1 ± 281.9 kcal	Yes	NA				Yes
Wu, 2010 (China)	75	APACHE II	16 ± 4.4 (mean ± SD)	14 ± 2.1	Yes	NA				NA				NA
Altintas, 2011 (Turkey)	76	APACHE II	22.6 ± 7.4 (mean ± SD)	20.03 ± 7.43	Yes	Mean daily energy intake	16.69 ± 4.71	11.62 ± 4.83 kcal/kg	No	Mean daily protein intake	0.74 ± 0.26 g/kg	0.45 ± 0.26 g/kg	No	Yes
Arbeloa, 2011 (Spain)	77	APACHEI II	18.5 ± 7.38 (mean ± SD)	18.8 ± 8.7	Yes	Mean daily energy intake	1365 ± 65.7 kcal/d	697.8 ± 49.6	No	NA				NA
Davies, 2011 (Australia and New Zealand)	78	APACHE II	17 ± 2 (mean ± SD)	16 ± 1.35	Yes	NA				NA				NA
Justo Meirelles, 2011 (Brazil)	79	APACHE II	13 (7-21) [mean (range)]	14 (8 – 22)	Yes	Total energy intake during 5 days	6586 ±1052 kcal	5958 ± 3619 kcal	Yes	Total protein intake 5 days	NA	NA	No	Yes
Aydogmus, 2012 (Turkey)	80	APACHE II	21.1 ± 5.9 (mean ± SD)	20.4 ± 4.7	Yes	NA				NA				NA
Elke, 2013	81	APACHE II	19.6 (15.6-23.4)	20 (17-24)	Yes	Mean daily	17.3 kcal/kg	11.8 kcal/kg	No	Mean daily	0.64 g/kg	0.43 g/kg	No	Yes

(Germany)			[mean (interquartile range)			energy intake				protein inatke				
Wang, 2013 (China)	82	APACHE II	14.6 ± 3.6 (mean	13.1 ± 3	Yes	NA				NA				NA
Bito, 2013 (Japan)	83	NA				NA				NA				NA
Harvey, 2014 (United Kingdom)	7	APACHE II	19.6 ± 6.9 (mean ± SD)	19.6 ± 6.9	Yes	Mean daily energy intake	21.3 ± 7.7 kcal/kg	18.5 ± 7.7 kcal/kg	Yes	Mean daily protein intake	0.7 ± 0.3 g/kg	0.6 g/kg	Yes	Yes
Reignier, 2015 (France)	84	SAPS II	46 (35-60) [median (interquartile range)	51 (40 – 64)	No	NA				NA				NA
Takesue, 2015 (Japan)	85	NA				Mean daily energy intake first 7 days	19.3 ± 3.5 (mean ± SD)	17.6 ± 2.5	Yes	NA				Yes
Fan, 2016 (China)	86	NA				NA				NA				NA
Gavri, 2016 (Greece)	87	APACHE II	15.58 (12.37 – 20.79) [median (IQR)]	17 (11 – 21)	Yes	Mean daily energy intake	1246 (765-1932) kcal	415 (157-687) kcal	No	Mean daily protein intake	70.2 (41.6-104.26) g	22 (10 – 34) g	No	Yes
Perinel, 2016 (France)	88	NA				Mean daily energy intake	26 kcal/kg	14.5 kcal/kg	No	Mean daily protein intake	NA	NA	Yes	NA
Zhang, 2016 (China)	89	NA				NA				NA				NA
Theodorakopoulou, 2016 (Greece)	90	NA				NA				NA				NA
Chen, 2017 (China)	91	NA				NA								NA
Yang, 2017 (China)	92	APACHE II	22 (18.3 – 24) [median (IQR)]	21 (18 – 25)	Yes	Mean daily energy intake first 7 days	1271 ± 359 kcal	1134 ± 412 kcal	Yes	NA				NA
Terzi, 2017 (France)	93	SAPS II	35.5 (26 – 45) [median (IQR)]	35.7 (27.9 – 45.3)	Yes	NA				NA				NA
Wischmeyer, 2017 (United States)	94	APACHE II	20.5 ± 6.4 (mean ± SD)	20.8 ± 7	Yes	Mean daily energy intake (7 days)	1844 ± 420 kcal	1728 ± 444 kcal	Yes	Mean daily protein intake (7 days)	106 ± 30g	100 ± 31g	Yes	Yes
Pierantozzi, 2017 (Italy)	95	NA				NA				NA				NA

Reignier, 2018 (France)	96	SAPS II	59 ± 19 (mean ± SD)	61 ± 20	Yes	Mean daily energy intake	19.6 ± 5.3 kcal/kg	17.8 ± 5.5 kcal/kg	No	Mean daily protein intake	0.8 ± 0.2 g/kg	0.7 ± 0.2 g/kg	No	Yes
Riddley, 2018 (Australia)	97	APACHE II	18 ± 7 (mean ± SD)	19 ± 7	Yes	Mean daily energy intake	24.9 ± 6.4 kcal/kg	16.8 ± 8.2 kcal/kg	No	Mean daily protein intake	1 ± 0.3 g/kg	0.6 ± 0.3 g/kg	No	Yes
Wang, 2018 (China)	98	NA				NA				NA				Yes
Guo, 2019 (China)	99	APACHE II	12.8 ± 3.1 (mean ± SD)	9.2 ± 4.7	No	Mean daily energy intake	34 ± 6.2 kcal/kg	36.2 ± 7.1	Yes	Mean daily protein intake	1.2 ± 0.6 g/kg/d	1 ± 0.5	Yes	Yes
Berger, 2019 (Switzerland)	100	APACHE II	25 (17 – 26) [Median (Q1 – Q3)]	23 (19.2 – 27.8)	Yes	Mean daily energy intake	24.3 kcal/kg	17.8 kcal/kg	No	Mean daily protein intake	1.11 g/kg/d	0.69 g/kg/d	No	Yes
Hui, 2019 (China)	101	APACHE II	APACHE II = 9.3 ± 0.3	APACHE II = 10 ± 0.4	Yes	NA				NA				NA
Bouleuc, 2020 (France)	102	ECOG	NA	NA	Yes	NA				NA				NA
Groningen, 2020 (Netherlands)	103	NA				NA				NA				NA

NA: not available; IQR: interquartile range U: uncertain; H: high: L: low; SD: standard deviation; kcal: kilocalories; TPN: total parenteral nutrition; EN: enteral nutrition; SPN: supplemental parenteral nutrition; kg: kilogram; g: gram: d: day

Supplementary Figure 1: Risk of bias



Supplementary Figure 2: Risk of bias.

Supplementary Table 4: Quality of observational studies - Newcastle-Ottawa Scale:

Study	Selection 1	Selection 2	Selection 3	Selection 4	Comparabiliy 1	Comparability 2	Outcome 1	Outcome 2	Outcome 3	Quality	Reference
Sedman, 1995	*	*	*	*			*	*	*	POOR	43
Ávila, 2006	*	*	*	*	*	*	*	*	*	GOOD	64
Modena, 2006	*	*	*	*	*	*	*	*		GOOD	67
Ryan, 2007	*	*	*	*	*		*	*	*	GOOD	69
Elke, 2008	*	*	*	*	*	*	*	*	*	GOOD	70
Matsushima, 2010	*	*	*	*		*	*	*	*	GOOD	74
Arbeloa, 2011	*	*	*	*			*	*	*	POOR	77
Davies, 2011	*	*	*	*			*	*	*	POOR	78
Elke, 2013	*	*	*	*	*	*	*	*	*	GOOD	81
Bito, 2013	*		*	*	*	*	*	*	*	GOOD	83
Reignier, 2015	*	*	*	*	*	*	*	*	*	GOOD	84
Gavri, 2016	*	*	*	*	*	*	*	*	*	GOOD	87
Terzi, 2017	*	*	*	*	*	*	*	*	*	GOOD	93
Pierantozzi, 2017	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	95
Yang, 2019	*	*	*	*	*	*	*	*	*	GOOD	92
Guo, 2019	*	*	*	*	*	*	*	*	*	GOOD	99

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domais

NA: Data not available for quality assessment (abstract only)

Supplementary Table 5: Relevant outcomes of the included trials of parenteral nutrition versus non-parenteral nutrition.

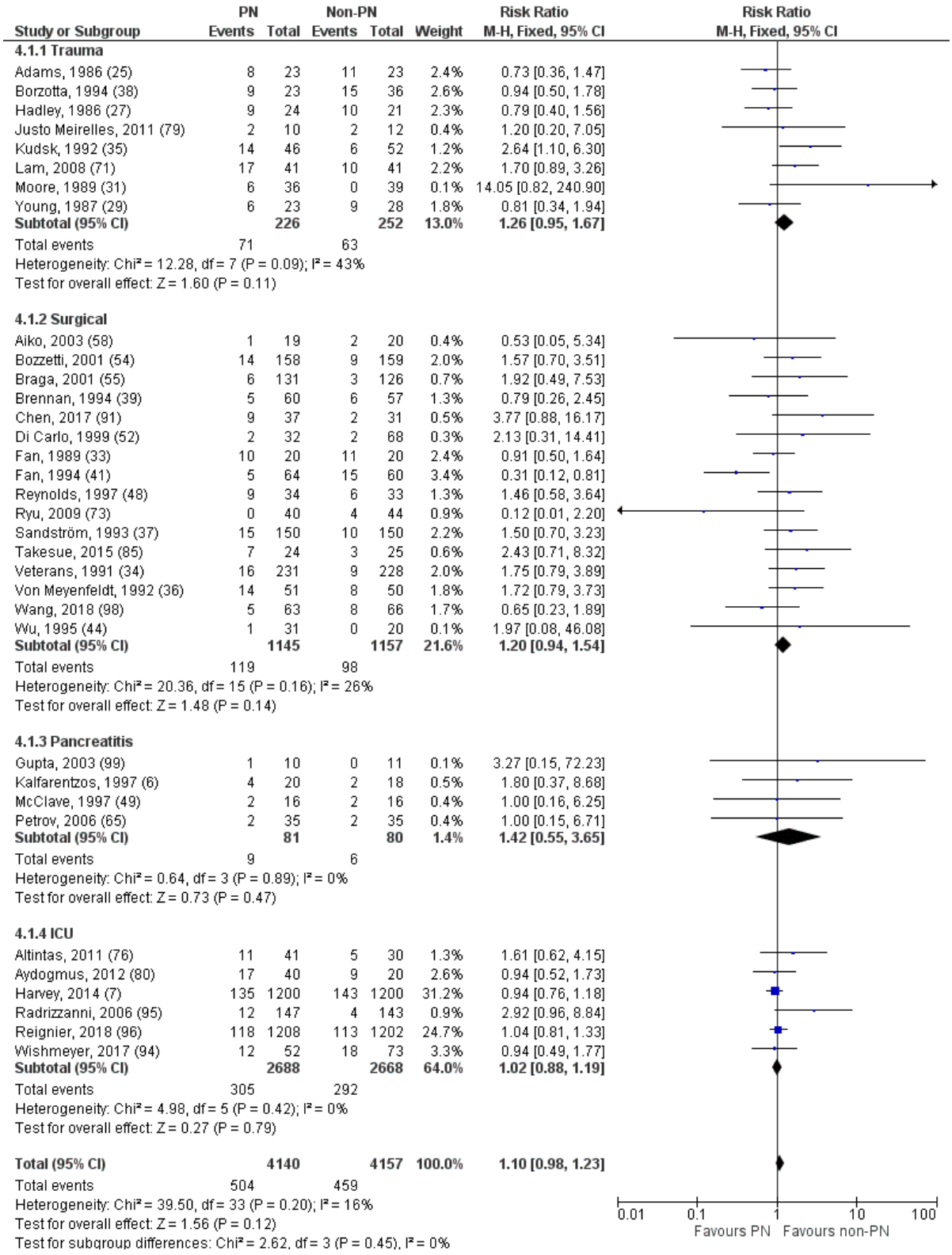
		Parenteral Nutrition						Non-Parenteral Nutrition					
Study	Ref	Infection	Pneumonia	Abdominal	Catheter	Mortality		Infection	Pneumonia	Abdominal	Catheter	Mortality	
Lim, 1981 (China)	4	5			2	1	**12**	5			0	2	**12**
Rapp, 1983 (United States)	5					3	**20**					9	**18**
Adams, 1986 (United States)	25		8	2	2	3	**23**		11	1	0	1	**23**
McIntyre, 1986 (England)	26					1	**27**					1	**20**
Hadley, 1986 (United States)	27	17	9			2	**24**	15	10			3	**21**
Fasth, 1987 (Sweden)	28					1	**48**					1	**44**
Young, 1987 (United States)	29	4	6			10	**23**	5	9			10	**28**
Bellantone, 1987 (Italy)	30	12				1	**49**	18				2	**51**
Moore, 1989 (United States)	31	11	6	2	2		**36**	5	0	1	0		**39**
Woolfson, 1989 (England)	32					8	**62**					8	**60**
Fan, 1989 (China)	33		10			6	**20**		11			6	**20**
VETERANS, 1991 (United States)	34	27	16	2		14	**231**	13	9	2		10	**228**
Kudsk, 1992 (United States)	35	20	14	6	6		**46**	12	6	1	1		**52**
Meyenfeldt, 1992 (Netherlands)	36		14	4		2	**51**		8	4		4	**50**
Sandström, 1993 (Sweden)	37	43	15			12	**150**	24	10			10	**150**
Borzotta, 1994 (United States)	38		9	1	2	1	**23**		15	0	3	5	**36**
Brennan, 1994 (United States)	39		5	23	5	4	**60**		6	8	1	1	**57**
Dunham, 1994 (United States)	40					4	**25**					1	**12**
Fan, 1994 (Hong Kong)	41	11	5	5	1	5	**64**	22	15	7	0	9	**60**
Wicks, 1994 (England)	42	7				1	**10**	10				1	**14**
Sedman, 1995 (England)	43	4				2	**28**	15				6	**175**
Wu, 1995 (Taiwan)	44	4	1	2		3	**31**	0	0	0		0	**20**
Hadfield, 1996 (England)	45					6	**11**					2	**13**

		Parenteral Nutrition						Non-Parenteral Nutrition					
Study	Ref	Infection	Pneumonia	Abdominal	Catheter	Mortality		Infection	Pneumonia	Abdominal	Catheter	Mortality	
Hernandez-Aranda, 1996 (Mexico)	46				3	6	**12**				2	3	**10**
Baigrie, 1996 (Australia)	47				7	6	**47**				0	4	**50**
Reynolds, 1997 (England)	48	20	9	6	3	1	**34**	13	6	3	1	2	**33**
Kalfarentzos, 1997 (Greece)	6	10	4	4	2	2	**20**	5	2	2	0	1	**18**
McClave, 1997 (United States)	49	2	2		2	0	**16**	2	2		0	0	**16**
Windsor, 1998 (United Kingdom)	50	3				2	**18**	0				0	**16**
Hu, 1998 (United States)	51	5					**19**	8					**21**
Di Carlo, 1999 (Italy)	52	8	2	3		2	**32**	9	2	4		1	**68**
Bauer, 2000 (France)	53	28				17	**60**	23				18	**60**
Bozzeti, 2001 (Italy)	54	42	14			5	**158**	25	9			2	**159**
Braga, 2001 (Italy)	55	30	6	16		4	**131**	25	3	13		3	**126**
Abou-Assi, 2002 (United States)	56				9	6	**27**				1	8	**26**
Oláh, 2002 (Hungary)	57	13				4	**48**	5				2	**41**
Aiko, 2003 (Japan)	58	4	1			0	**19**	5	2			0	**20**
Bertolini, 2003 (Italy)	59					5	**21**					5	**21**
Gupta, 2003 (United Kingdom)	60	2	1		1	0	**10**	1	0		0	0	**11**
Xian-Li, 2004 (China)	61			5		3	**41**			8		10	**23**
Louie, 2005 (Canada)	62			5	2	3	**18**			1	0	0	**10**
Zhang, 2005 (China)	63	2		1		0	**20**	0		0		0	**20**
Ávila, 2006 (Mexico)	64			12		6	**81**			7		5	**33**
Petrov, 2006 (Russia)	65		2	16	5	12	**35**		2	7	0	2	**35**
Radrizzani, 2006 (Italy)	66	19	12	2		20	**147**	7	4	1		17	**143**
Modena, 2006 (Peru)	67			32		15	**43**			9		2	**44**
Casas, 2007 (Spain)	68	5		2	2	2	**11**	1		0	0	0	**11**
Ryan, 2007 (Ireland)	69	6	3			3	**38**	3	4			0	**52**
Elke, 2008 (Germany)	70					157	**278**					48	**121**
Lam, 2008 (Viet Nam)	71		17			15	**41**		10			6	**41**
Doley, 2009 (India)	72	15				4	**25**	16				5	**25**

		Parenteral Nutrition						Non-Parenteral Nutrition					
Study	**Ref**	Infection	Pneumonia	Abdominal	Catheter	Mortality		Infection	Pneumonia	Abdominal	Catheter	Mortality	
Ryu, 2009 (South Korea)	73	5	0		1		**40**	7	4		0		**44**
Matsushima, 2010 (United States)	74	19	11		7		**35**	57	45		8		**120**
Wu, 2010 (China)	75			39		23	**54**			12		6	**53**
Altintas, 2011 (Turkey)	76	13	11		4	20	**41**	7	5		2	13	**30**
Arbeloa, 2011 (Spain)	77		19				**60**		9				**42**
Davies, 2011 (Australia/New Zealand)	78					5	**18**					2	**27**
Justo Meirelles, 2011 (Brazil)	79	4	2			1	**10**	2	2			1	**12**
Aydogmus, 2012 (Turkey)	80		17				**40**		9				**20**
Elke, 2013 (Germany)	81	178				108	**267**	32				23	**86**
Wang, 2013 (China)	82			24		7	**60**			21		4	**123**
Bito, 2013 (Japan)	83	92				85	**146**	119				126	**364**
Harvey, 2014 (United Kingdom)	7		135		11	431	**1200**		143		9	450	**1200**
Reignier, 2015 (France)	84					153	**481**					450	**1380**
Takesue, 2015 (Japan)	85		7		1	0	**24**		3		1	0	**25**
Fan, 2016 (China)	86					21	**80**					12	**40**
Gavri, 2016 (Greece)	87					86	**203**					24	**46**
Perinel, 2016 (France)	88	42				7	**106**	40				2	**106**
Zhang, 2016 (China)	89	2					**60**	2					**60**
Theodorakopoulou, 2016 (Greece)	90					20	**69**					21	**77**
Chen, 2017 (China)	91		9	9		1	**37**		2	2		0	**31**
Yang, 2017 (China)	92		9	4	6	14	**88**		3	4	1	7	**95**
Terzi, 2017 (France)	93		9		3		**74**		80		20		**1001**
Wischmeyer, 2017 (United States)	94	14	12	4	7	8	**52**	23	18	0	0	17	**73**
Pierantozzi, 2017 (Italy)	95	18				12	**31**	21				13	**77**
Reignier, 2018 (France)	96	194	118		27	479	**1208**	173	113		29	498	**1202**
Riddley, 2018 (Australia)	97	18				16	**51**	16				11	**49**
Wang, 2018 (China)	98		5		8		**63**		8		0		**66**
Guo, 2019 (China)	99					55	**89**					0	**11**

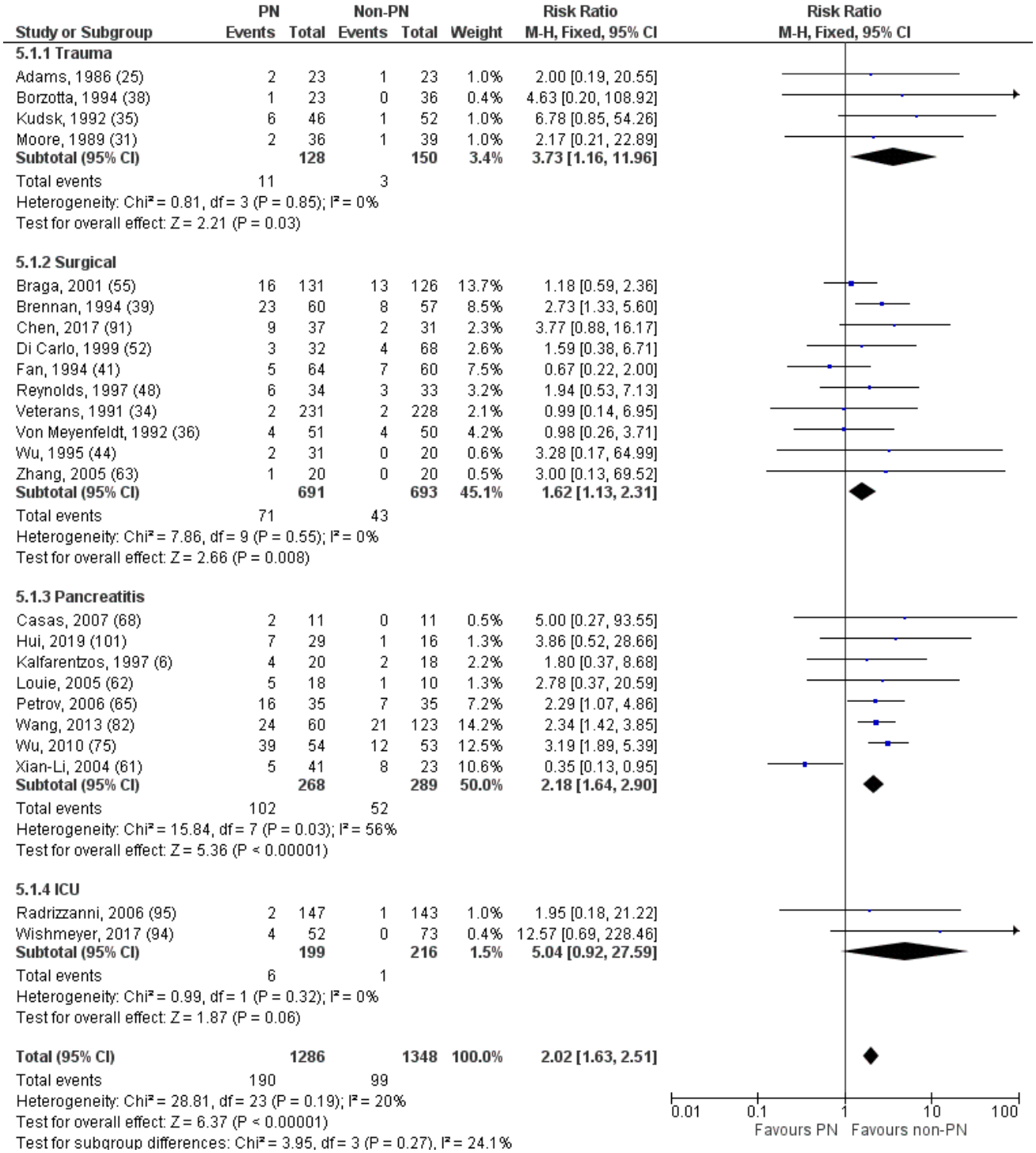
		Parenteral Nutrition						Non-Parenteral Nutrition					
Study	**Ref**	Infection	Pneumonia	Abdominal	Catheter	Mortality		Infection	Pneumonia	Abdominal	Catheter	Mortality	
Berger, 2019 (Switzerland)	100	0				0	**11**	**1**				1	**12**
Hui, 2019	101	7				5	**29**	**1**				1	**16**
Boulec, 2020 (France)	102					46	**70**					58	**78**
Groningen, 2020 (Netherlands)	103	7					**20**	**3**					**11**
Total number of events		992	555	231	131	1993		796	600	118	79	1974	
Total number of patients		3617	4435	1469	3256	6848	7341	3952	5467	1504	4289	7558	9034
%		27.4	12.5	15.7	4	29.1		20.1	10.9	7.8	1.8	26.1	
Number of studies		44	39	26	27	72	83	44	39	26	27	72	83

1. **Supplementary Figure 3. Forest plot for pneumonia in studies comparing parenteral nutrition (n = 34 RCTs) versus non-parenteral nutrition, stratified by study population.**



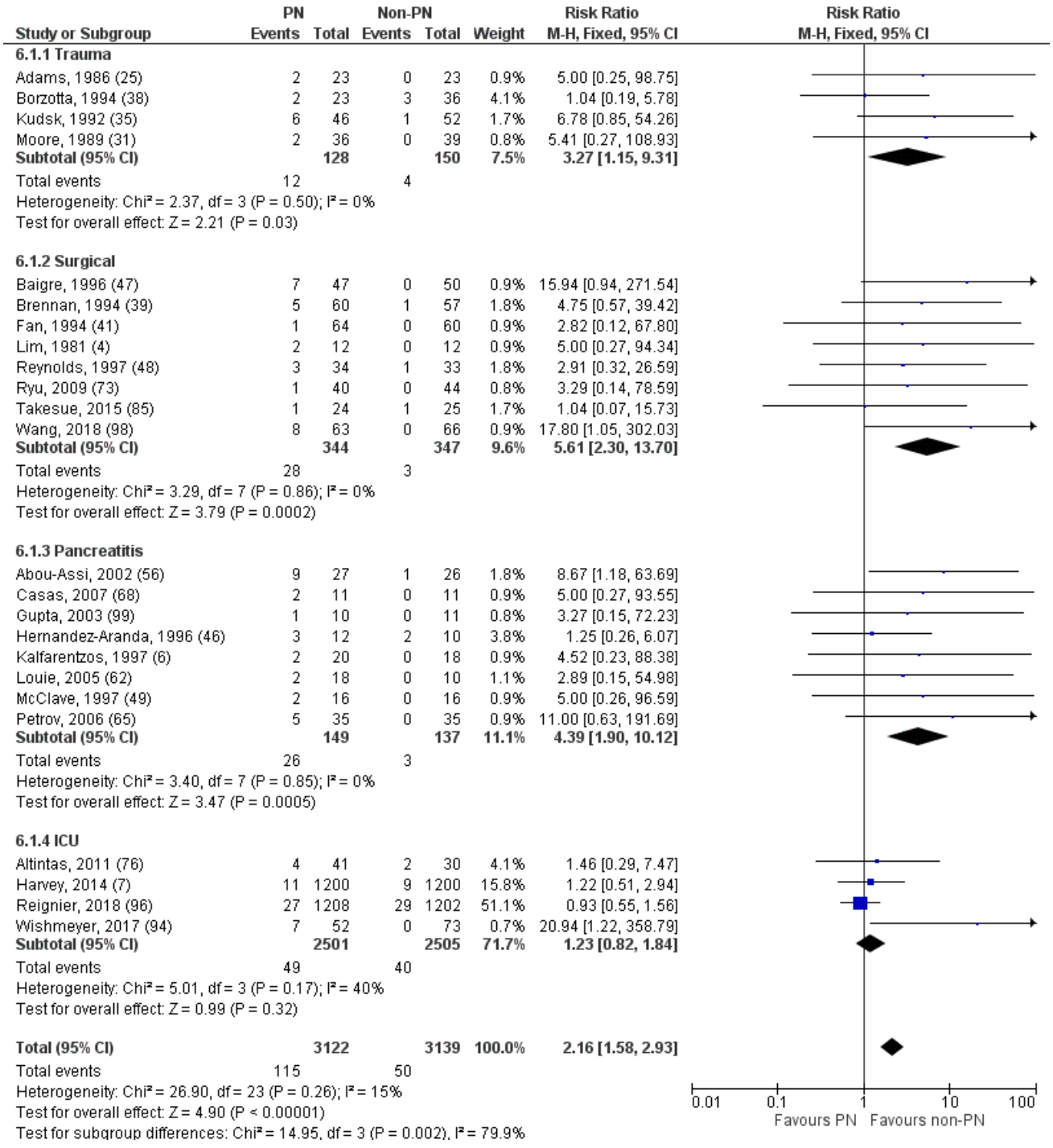
Fixed effects model of relative risk (95% confidence interval). PN: parenteral nutrition.

10. Supplementary Figure 4. Forest plot for abdominal infection in studies comparing parenteral nutrition (n = 24 RCTs) versus non-parenteral nutrition, stratified by study population.



Fixed effects model of relative risk (95% confidence interval). PN: parenteral nutrition.

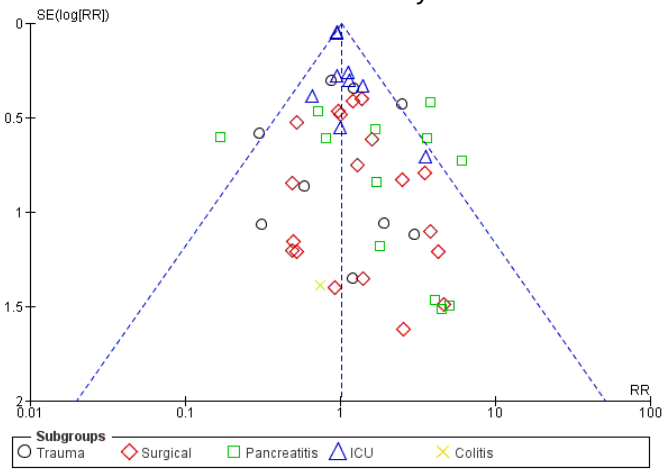
11. Supplementary Figure 5. Forest plot for catheter infection in studies comparing parenteral nutrition (n = 24 RCTs) versus non-parenteral nutrition, stratified by study population.



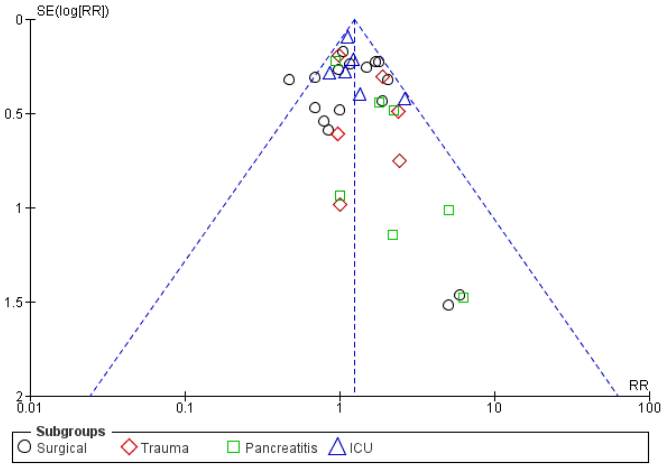
Fixed effects model of relative risk (95% confidence interval). PN: parenteral nutrition.

12. **Supplementary Results 1: Funnel plots diagram of publication bias of the meta-analyses of parenteral nutrition versus non-parenteral nutrition – all graphs with pseudo 95% confidence limits.**

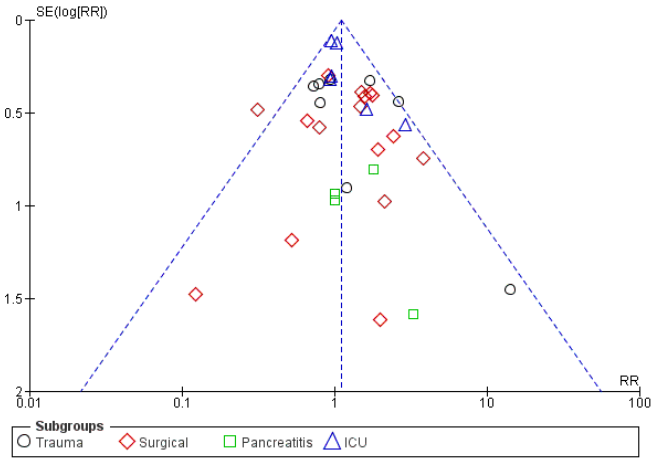
A. Mortality



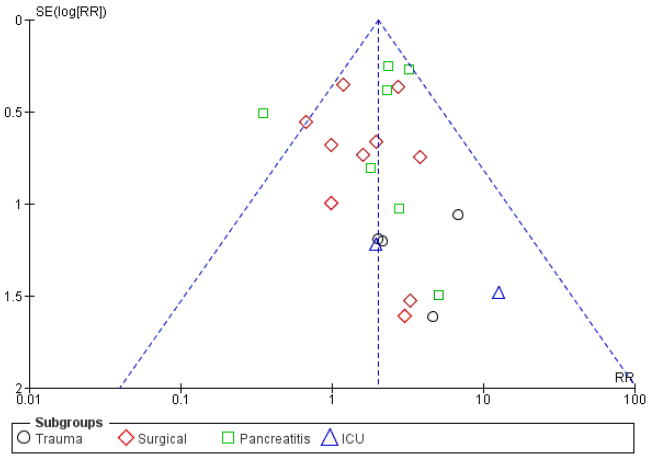
B. Infection



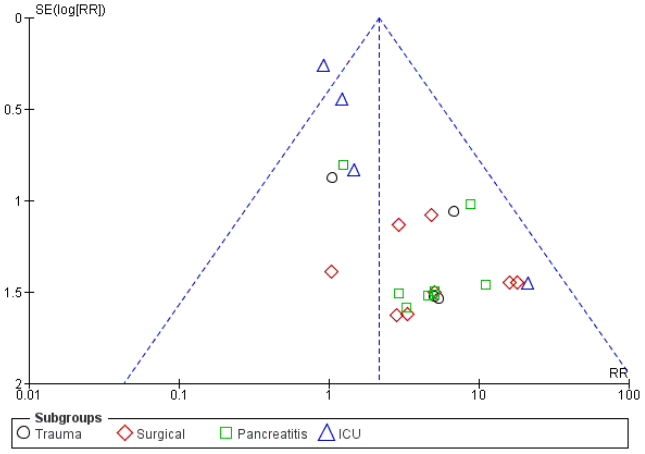
C. Pneumonia



D. Abdominal Infection

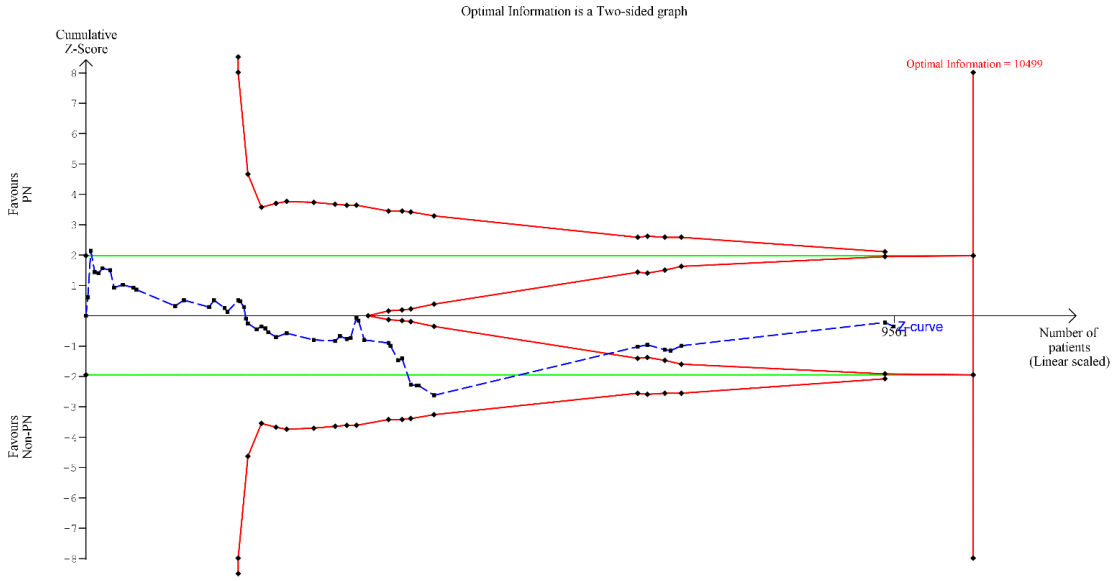


E. Catheter Infection

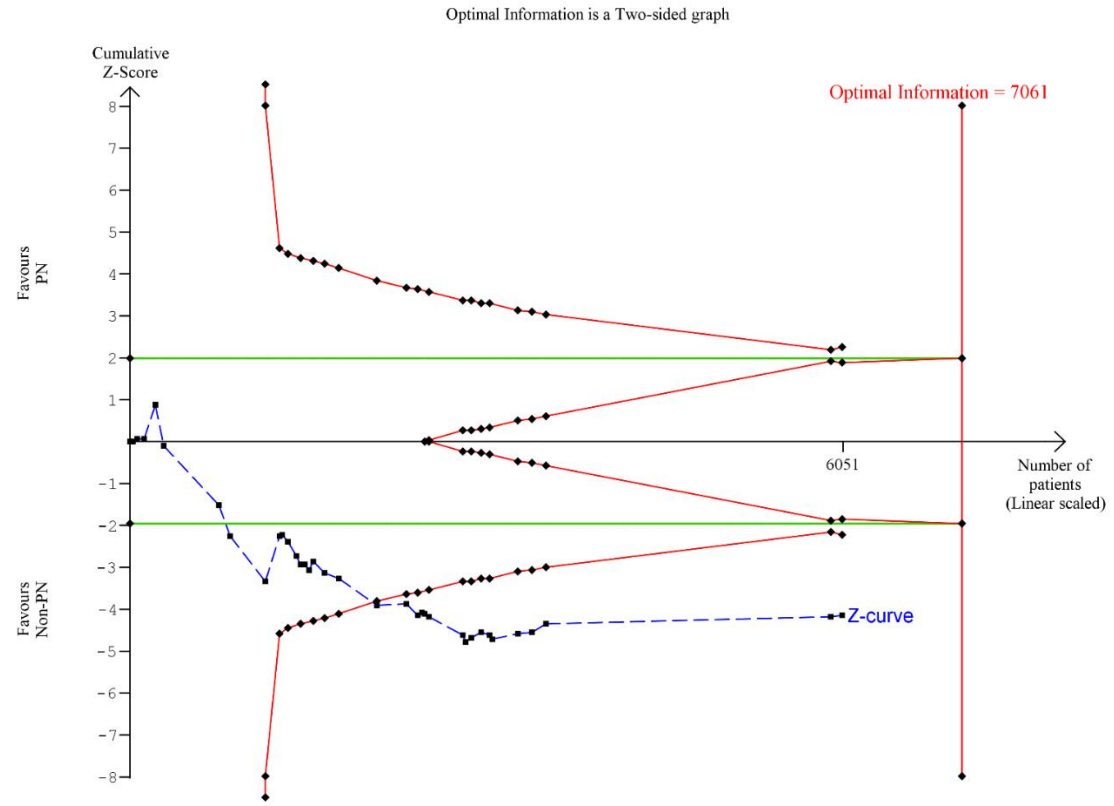


13. Supplementary Results 2: TSA graphic for outcomes of parenteral nutrition versus non- parenteral nutrition.

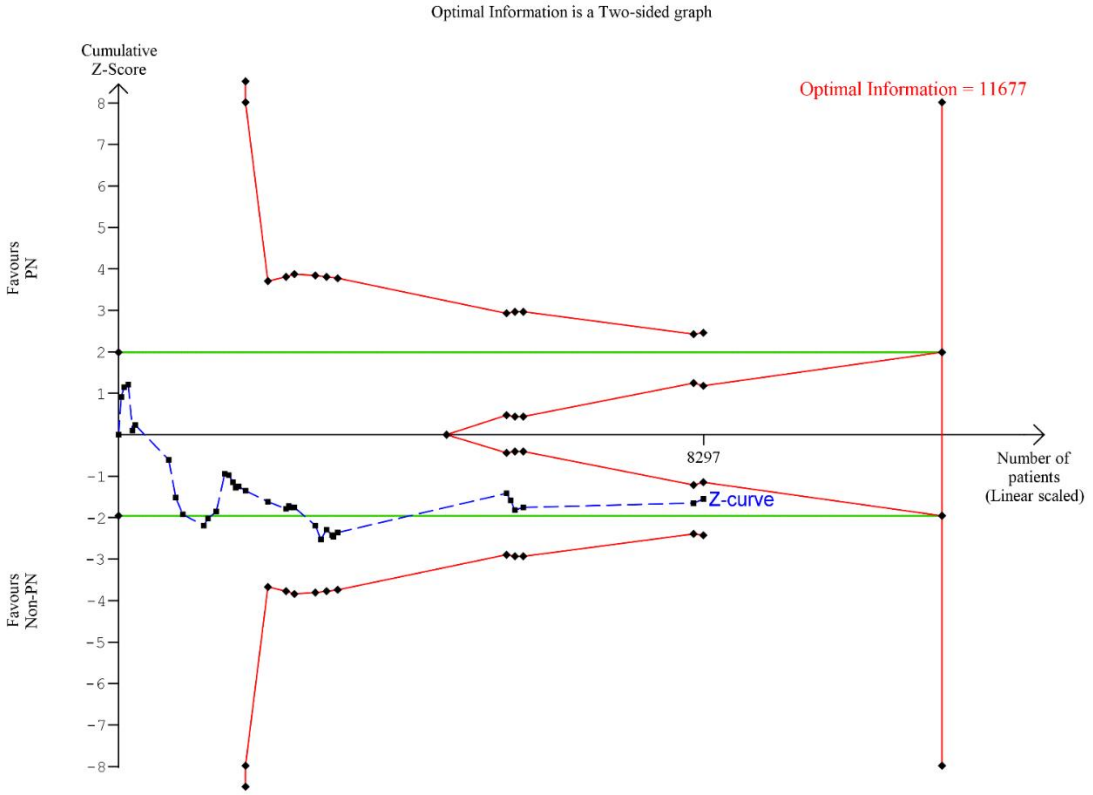
A) Mortality



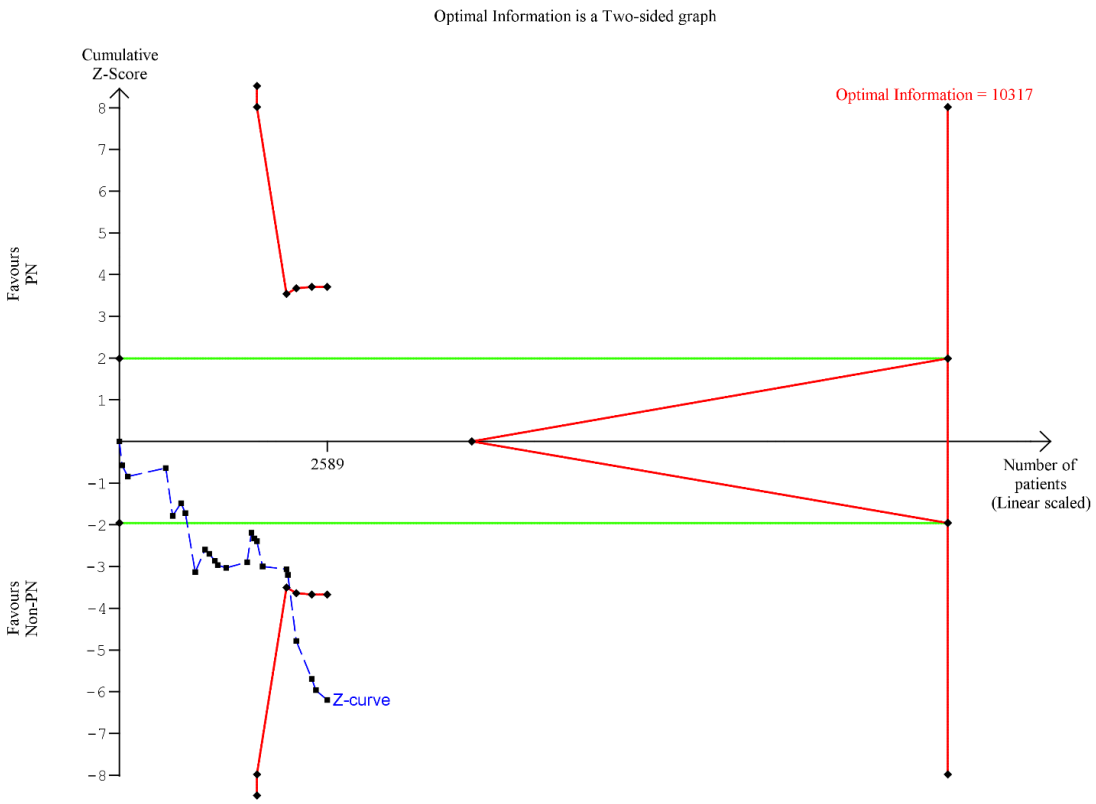
B) Infection



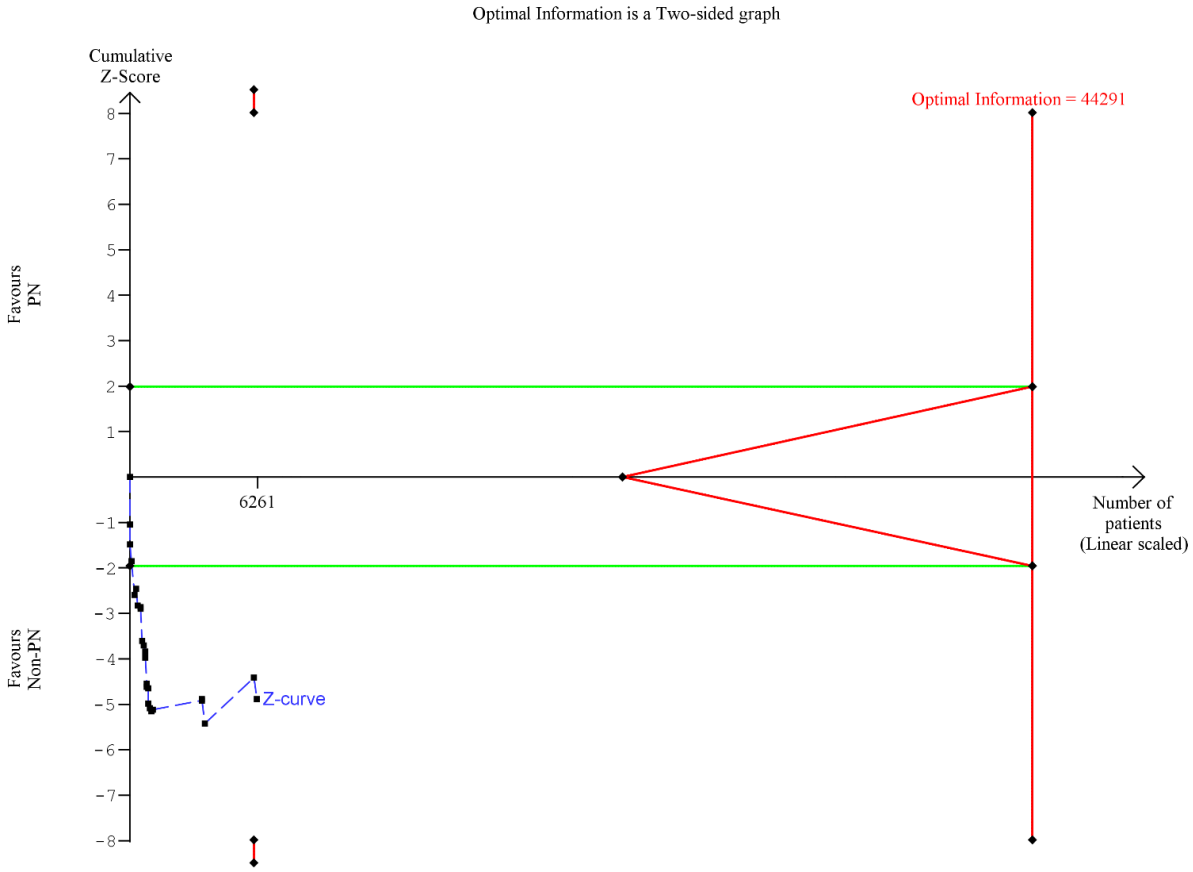
C) Pneumonia



D) Abdominal Infection



E) Catheter Infection



TSA for a relative risk of 20% for dichotomous variables and empirical variance and mean difference for continuous variables. Power of 80% and type 1 error of 5%.The dotted blue line represents the Z line (cumulative effect size), the red lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The horizontal continuous green line represent the conventional 95% CIs.

14. Supplementary Results 3: Sensitivity analyses of results from meta-analysis from studies comparing parenteral nutrition versus non-parenteral nutrition:

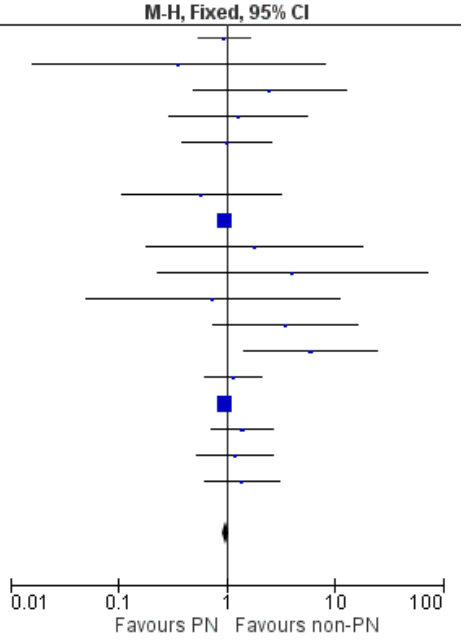
A. Mortality

1) Low bias studies

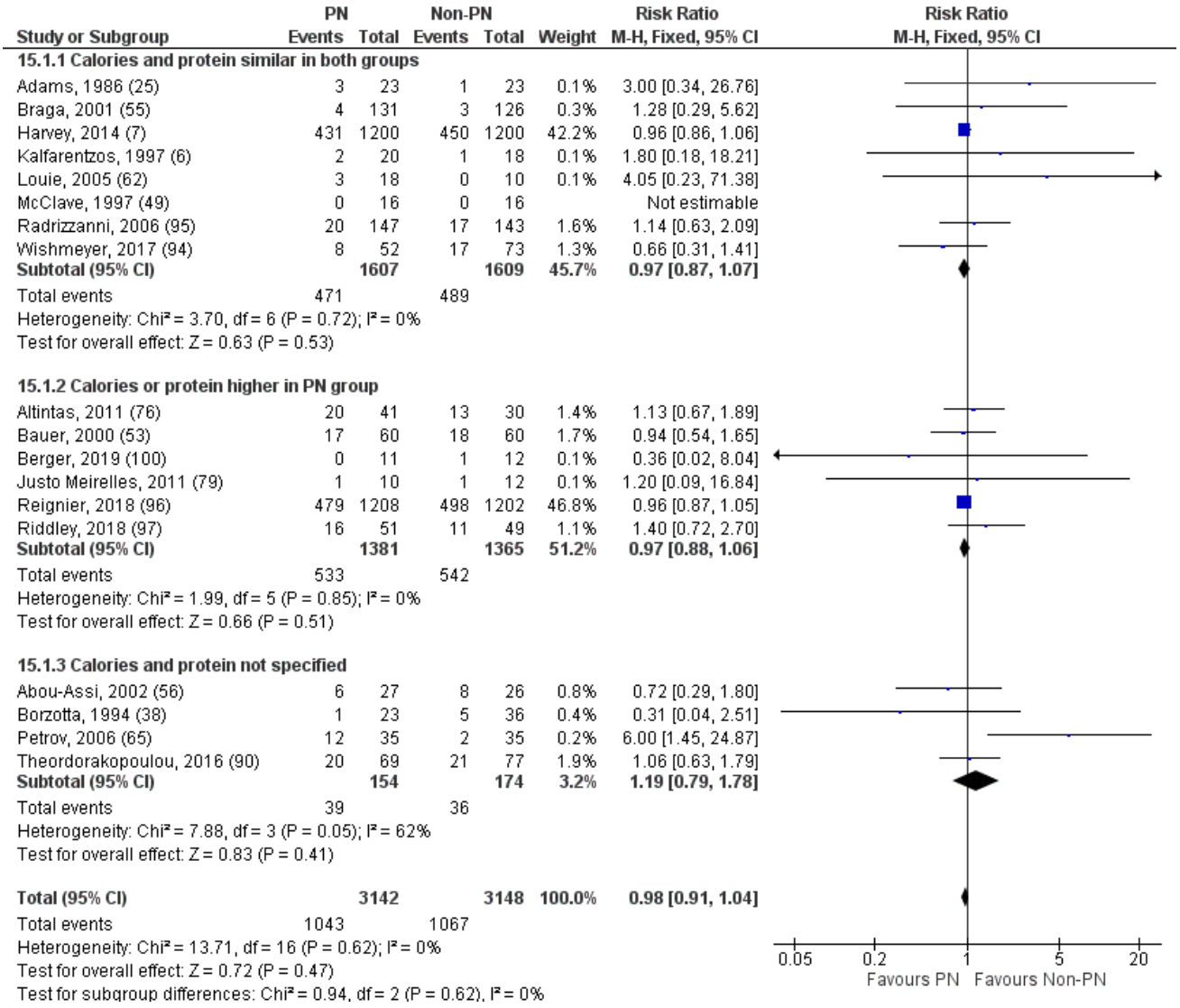
Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bauer, 2000 (53)	17	60	18	60	1.7%	0.94 [0.54, 1.65]
Berger, 2019 (100)	0	11	1	12	0.1%	0.36 [0.02, 8.04]
Bozzetti, 2001 (54)	5	158	2	159	0.2%	2.52 [0.50, 12.78]
Braga, 2001 (55)	4	131	3	126	0.3%	1.28 [0.29, 5.62]
Fan, 1989 (33)	6	20	6	20	0.6%	1.00 [0.39, 2.58]
Gupta, 2003 (99)	0	10	0	11		Not estimable
Hadley, 1986 (27)	2	24	3	21	0.3%	0.58 [0.11, 3.16]
Harvey, 2014 (7)	431	1200	450	1200	43.3%	0.96 [0.86, 1.06]
Kalfarentzos, 1997 (6)	2	20	1	18	0.1%	1.80 [0.18, 18.21]
Louie, 2005 (62)	3	18	0	10	0.1%	4.05 [0.23, 71.38]
McIntyre, 1986 (26)	1	27	1	20	0.1%	0.74 [0.05, 11.14]
Perinel, 2016 (86)	7	106	2	106	0.2%	3.50 [0.74, 16.46]
Petrov, 2006 (65)	12	35	2	35	0.2%	6.00 [1.45, 24.87]
Radrizzanni, 2006 (95)	20	147	17	143	1.7%	1.14 [0.63, 2.09]
Reignier, 2018 (96)	479	1208	498	1202	48.1%	0.96 [0.87, 1.05]
Riddley, 2018 (97)	16	51	11	49	1.1%	1.40 [0.72, 2.70]
Sandström, 1993 (37)	12	150	10	150	1.0%	1.20 [0.53, 2.69]
Veterans, 1991 (34)	14	231	10	228	1.0%	1.38 [0.63, 3.05]
Total (95% CI)		**3607**		**3570**	**100.0%**	**0.99 [0.92, 1.06]**
Total events	1031		1035			

Heterogeneity: Chi² = 15.19, df = 16 (P = 0.51); I² = 0%

Test for overall effect: Z = 0.26 (P = 0.79)



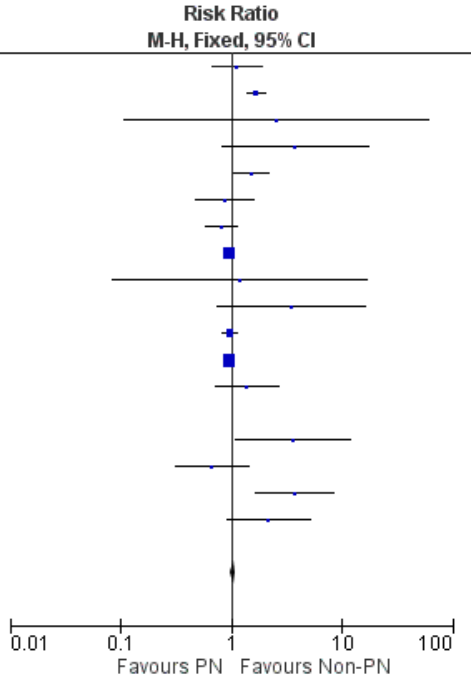
2) Severity score and glycemic control reported with calories and protein subgroup analyses.



3) Excluding older studies

Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Altintas, 2011 (76)	20	41	13	30	1.1%	1.13 [0.67, 1.89]
Bito, 2013 (83)	85	146	126	364	5.1%	1.68 [1.38, 2.05]
Chen, 2017 (91)	1	37	0	31	0.0%	2.53 [0.11, 59.90]
Davies, 2011 (78)	5	18	2	27	0.1%	3.75 [0.81, 17.28]
Elke, 2008 (70)	108	267	23	86	2.5%	1.51 [1.04, 2.21]
Fan, 1989 (33)	21	80	12	40	1.1%	0.88 [0.48, 1.59]
Gavri, 2016 (87)	86	203	24	46	2.8%	0.81 [0.59, 1.12]
Harvey, 2014 (7)	431	1200	450	1200	32.0%	0.96 [0.86, 1.06]
Justo Meirelles, 2011 (79)	1	10	1	12	0.1%	1.20 [0.09, 16.84]
Perinel, 2016 (86)	7	106	2	106	0.1%	3.50 [0.74, 16.46]
Reignier, 2015 (84)	153	481	450	1380	16.6%	0.98 [0.84, 1.13]
Reignier, 2018 (96)	479	1208	498	1202	35.5%	0.96 [0.87, 1.05]
Riddley, 2018 (97)	16	51	11	49	0.8%	1.40 [0.72, 2.70]
Takesue, 2015 (85)	0	24	0	25		Not estimable
Wang, 2013 (82)	7	60	4	123	0.2%	3.59 [1.09, 11.78]
Wishmeyer, 2017 (94)	8	52	17	73	1.0%	0.66 [0.31, 1.41]
Wu, 2010 (75)	23	54	6	53	0.4%	3.76 [1.67, 8.50]
Yang, 2017 (92)	14	88	7	95	0.5%	2.16 [0.91, 5.10]
Total (95% CI)		**4126**		**4942**	**100.0%**	**1.04 [0.98, 1.10]**
Total events	1465		1646			

Heterogeneity: Chi² = 59.23, df = 16 (P < 0.00001); I² = 73%
Test for overall effect: Z = 1.29 (P = 0.20)

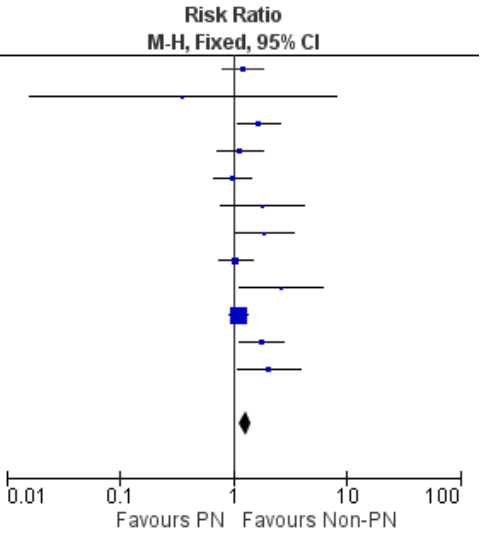


B. Infection

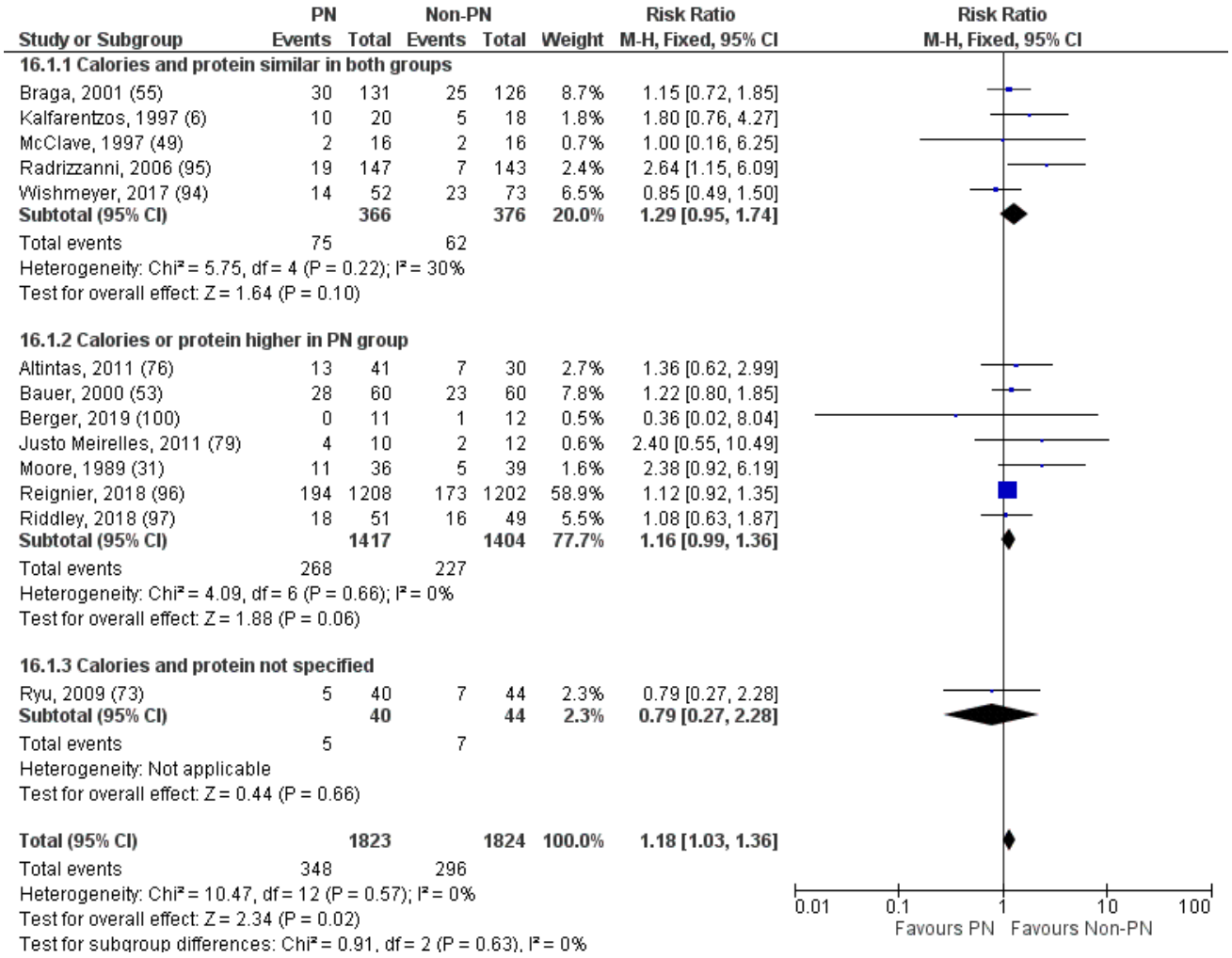
1) Low bias studies

Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bauer, 2000 (53)	28	60	23	60	6.3%	1.22 [0.80, 1.85]
Berger, 2019 (100)	0	11	1	12	0.4%	0.36 [0.02, 8.04]
Bozzetti, 2001 (54)	42	158	25	159	6.8%	1.69 [1.09, 2.63]
Braga, 2001 (55)	30	131	25	126	7.0%	1.15 [0.72, 1.85]
Hadley, 1986 (27)	17	24	15	21	4.4%	0.99 [0.68, 1.44]
Kalfarentzos, 1997 (6)	10	20	5	18	1.4%	1.80 [0.76, 4.27]
Kudsk, 1992 (35)	20	46	12	52	3.1%	1.88 [1.04, 3.42]
Perinel, 2016 (86)	42	106	40	106	11.0%	1.05 [0.75, 1.47]
Radrizzanni, 2006 (95)	19	147	7	143	1.9%	2.64 [1.15, 6.09]
Reignier, 2018 (96)	194	1208	173	1202	47.5%	1.12 [0.92, 1.35]
Sandström, 1993 (37)	43	150	24	150	6.6%	1.79 [1.15, 2.80]
Veterans, 1991 (34)	27	231	13	228	3.6%	2.05 [1.09, 3.87]
Total (95% CI)		**2292**		**2277**	**100.0%**	**1.29 [1.14, 1.45]**
Total events	472		363			

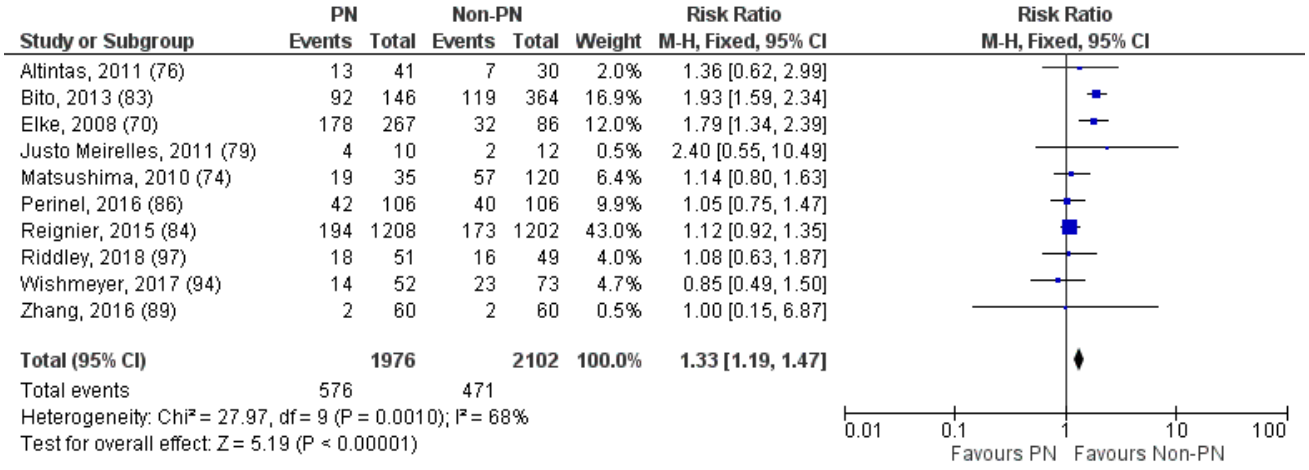
Heterogeneity: Chi² = 17.03, df = 11 (P = 0.11); I² = 35%
Test for overall effect: Z = 4.15 (P < 0.0001)



2) Severity score and glycemic control reported with calories and protein subgroup analyses.

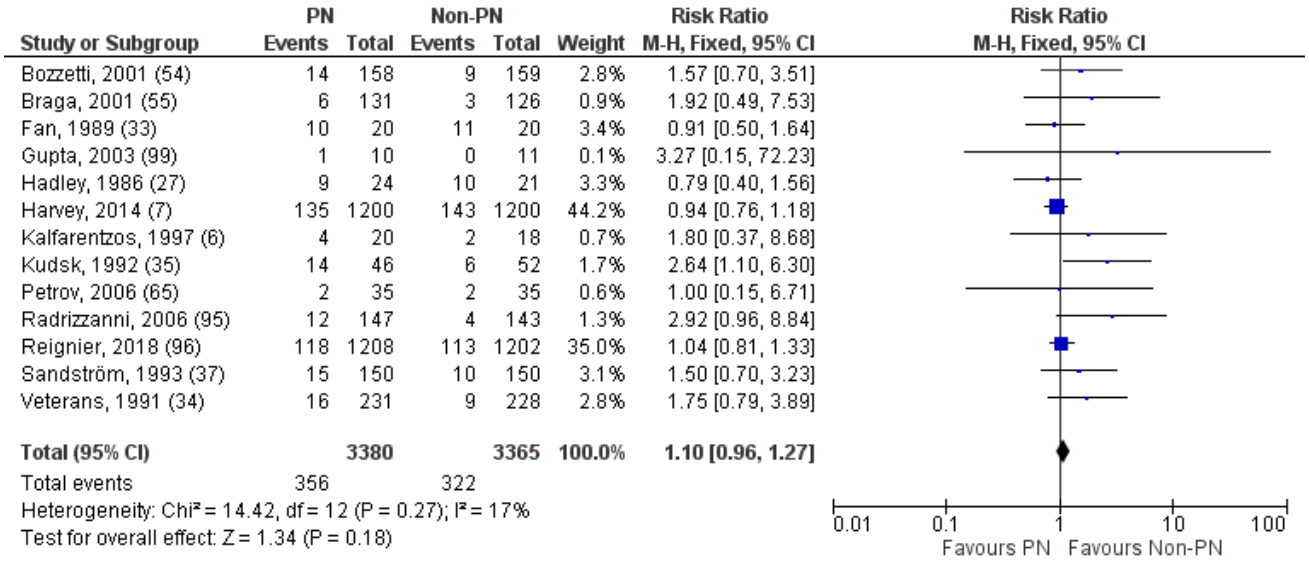


3) Excluding older studies

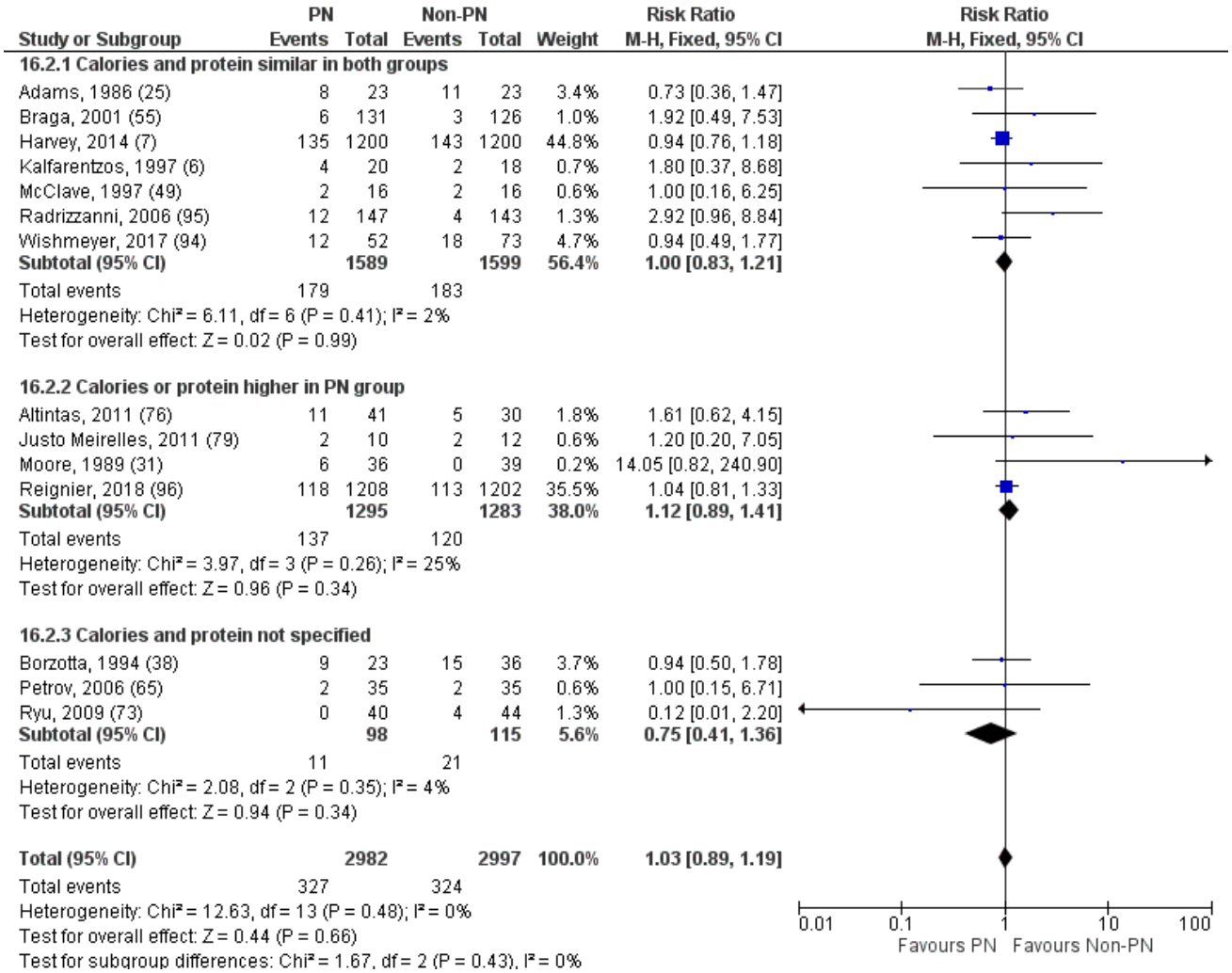


C. Pneumonia

1) Low bias studies



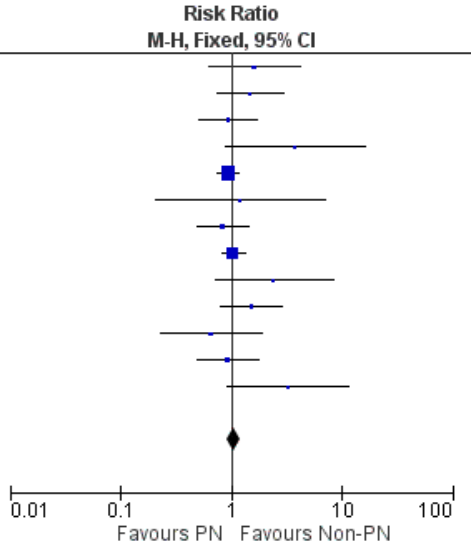
2) Severity score and glycemic control reported with calories and protein subgroup analyses.



3) Excluding older studies

Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Altintas, 2011 (76)	11	41	5	30	1.7%	1.61 [0.62, 4.15]
Arbeoloa, 2011 (77)	19	60	9	42	3.0%	1.48 [0.74, 2.94]
Aydogmus, 2012 (80)	17	40	9	20	3.4%	0.94 [0.52, 1.73]
Chen, 2017 (91)	9	37	2	31	0.6%	3.77 [0.88, 16.17]
Harvey, 2014 (7)	135	1200	143	1200	41.0%	0.94 [0.76, 1.18]
Justo Meirelles, 2011 (79)	2	10	2	12	0.5%	1.20 [0.20, 7.05]
Matsushima, 2010 (74)	11	35	45	120	5.8%	0.84 [0.49, 1.44]
Reignier, 2015 (84)	118	1208	113	1202	32.5%	1.04 [0.81, 1.33]
Takesue, 2015 (85)	7	24	3	25	0.8%	2.43 [0.71, 8.32]
Terzi, 2017 (93)	9	74	80	1001	3.2%	1.52 [0.80, 2.91]
Wang, 2013 (82)	5	63	8	66	2.2%	0.65 [0.23, 1.89]
Wishmeyer, 2017 (94)	12	52	18	73	4.3%	0.94 [0.49, 1.77]
Yang, 2017 (92)	9	88	3	95	0.8%	3.24 [0.91, 11.58]
Total (95% CI)		**2932**		**3917**	**100.0%**	**1.06 [0.92, 1.21]**
Total events	364		440			

Heterogeneity: Chi² = 13.35, df = 12 (P = 0.34); I² = 10%
Test for overall effect: Z = 0.81 (P = 0.42)

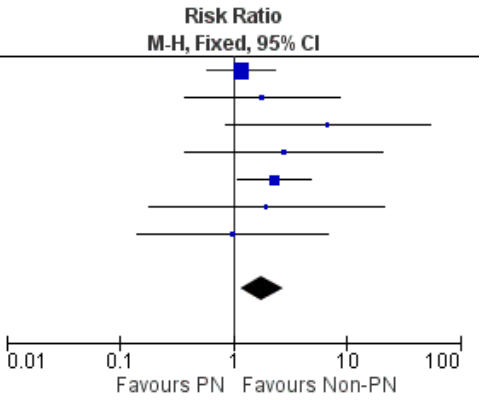


D. Abdominal Infection

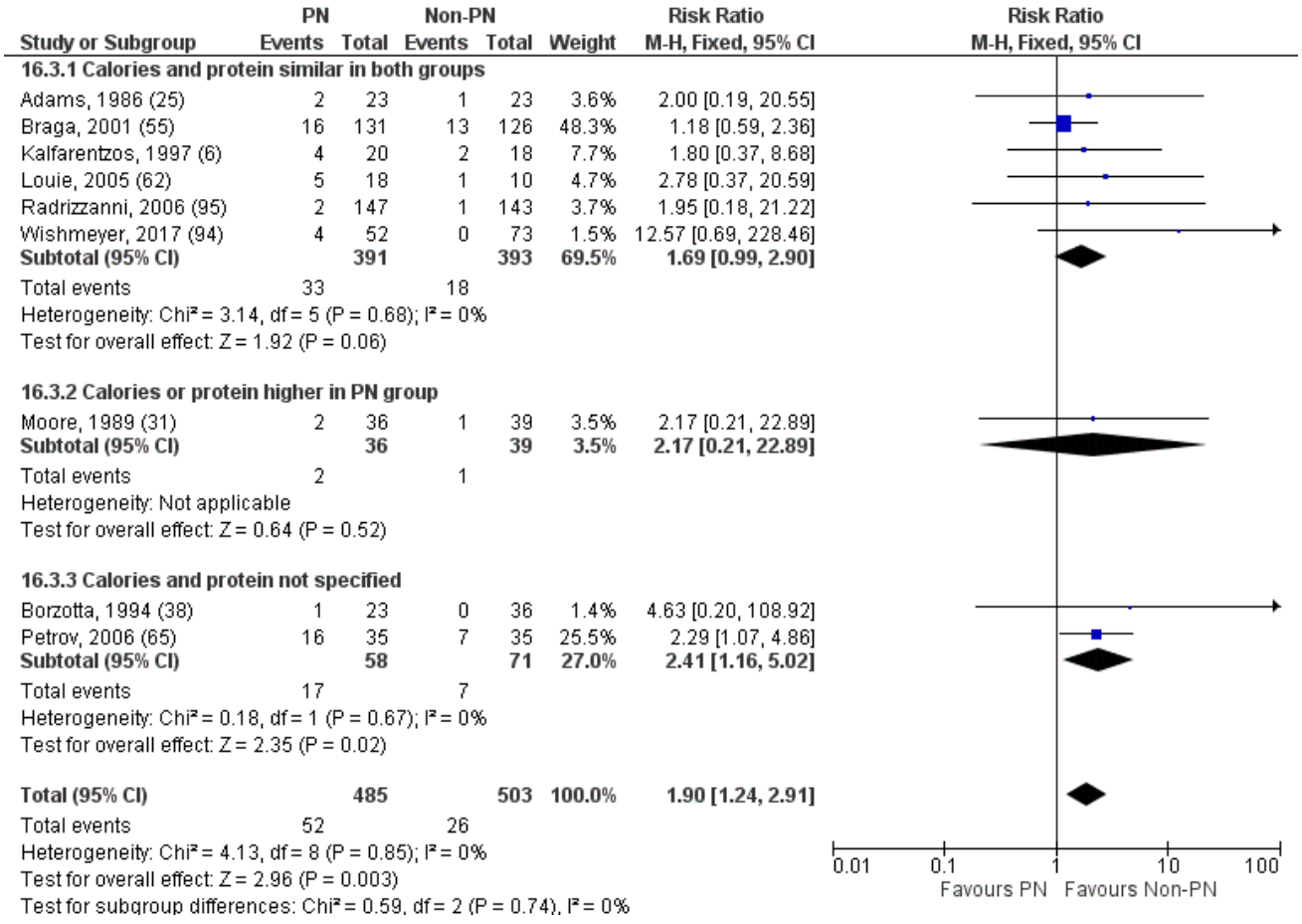
1) Low bias studies

Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Braga, 2001 (55)	16	131	13	126	48.0%	1.18 [0.59, 2.36]
Kalfarentzos, 1997 (6)	4	20	2	18	7.6%	1.80 [0.37, 8.68]
Kudsk, 1992 (35)	6	46	1	52	3.4%	6.78 [0.85, 54.26]
Louie, 2005 (62)	5	18	1	10	4.7%	2.78 [0.37, 20.59]
Petrov, 2006 (65)	16	35	7	35	25.4%	2.29 [1.07, 4.86]
Radrizzanni, 2006 (95)	2	147	1	143	3.7%	1.95 [0.18, 21.22]
Veterans, 1991 (34)	2	231	2	228	7.3%	0.99 [0.14, 6.95]
Total (95% CI)		**628**		**612**	**100.0%**	**1.79 [1.16, 2.75]**
Total events	51		27			

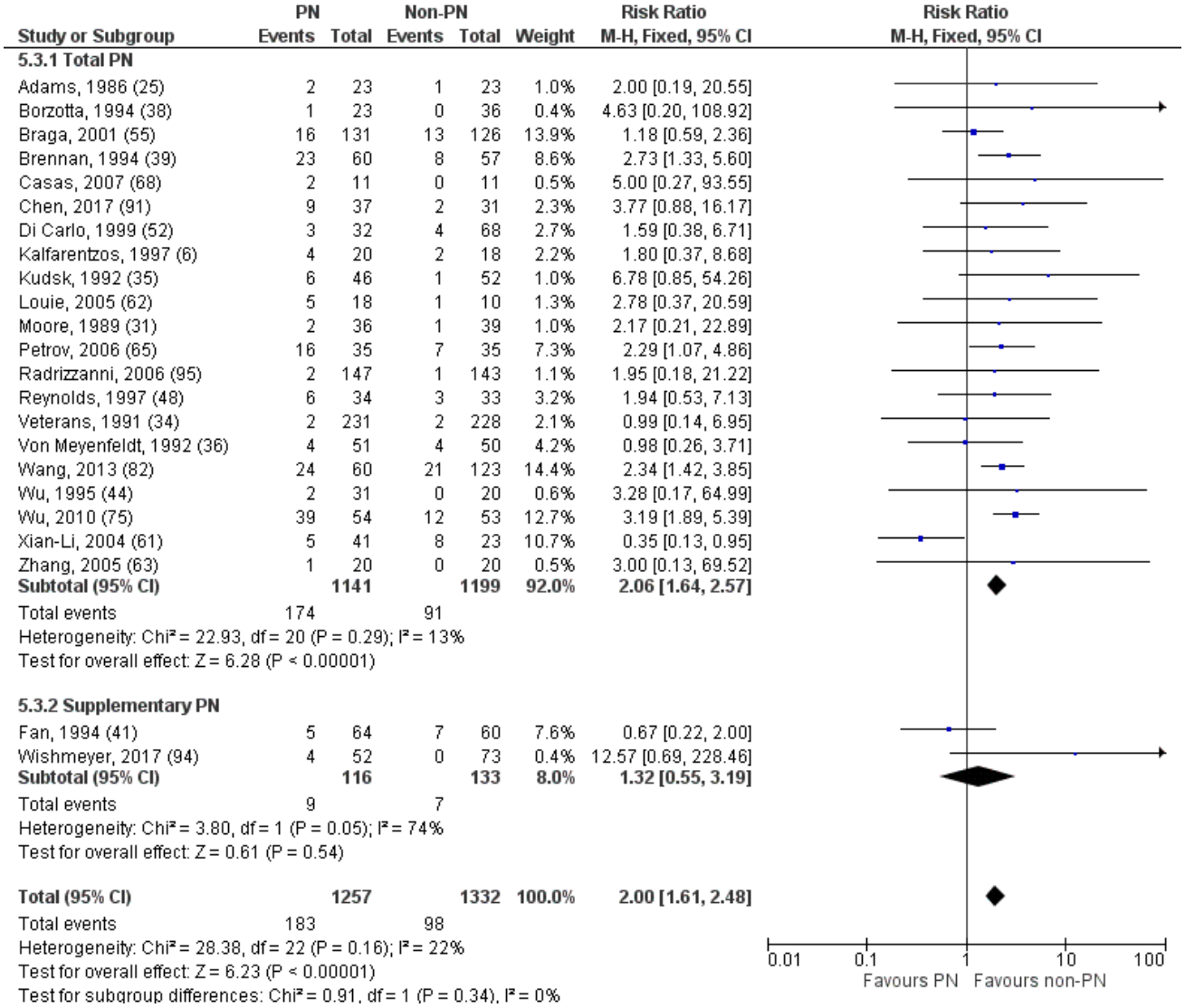
Heterogeneity: Chi² = 3.91, df = 6 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.64 (P = 0.008)



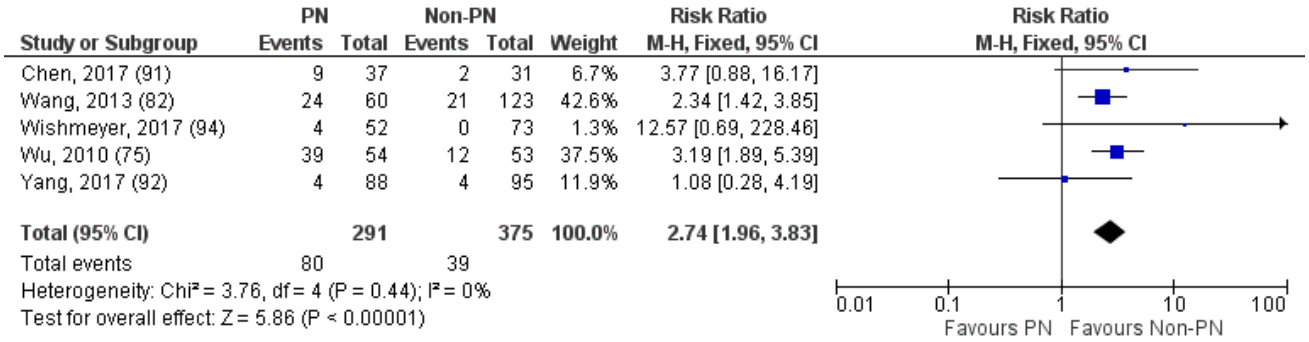
2) Severity score and glycemic control reported with calories and protein subgroup analyses.



3) Exploratory analysis comparing total vs. supplementary PN.

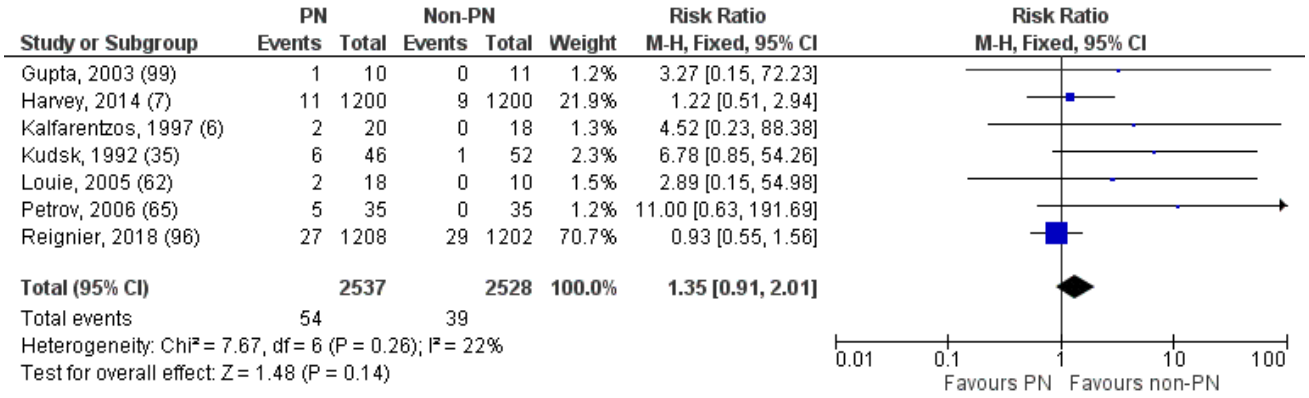


4) Excluding older studies

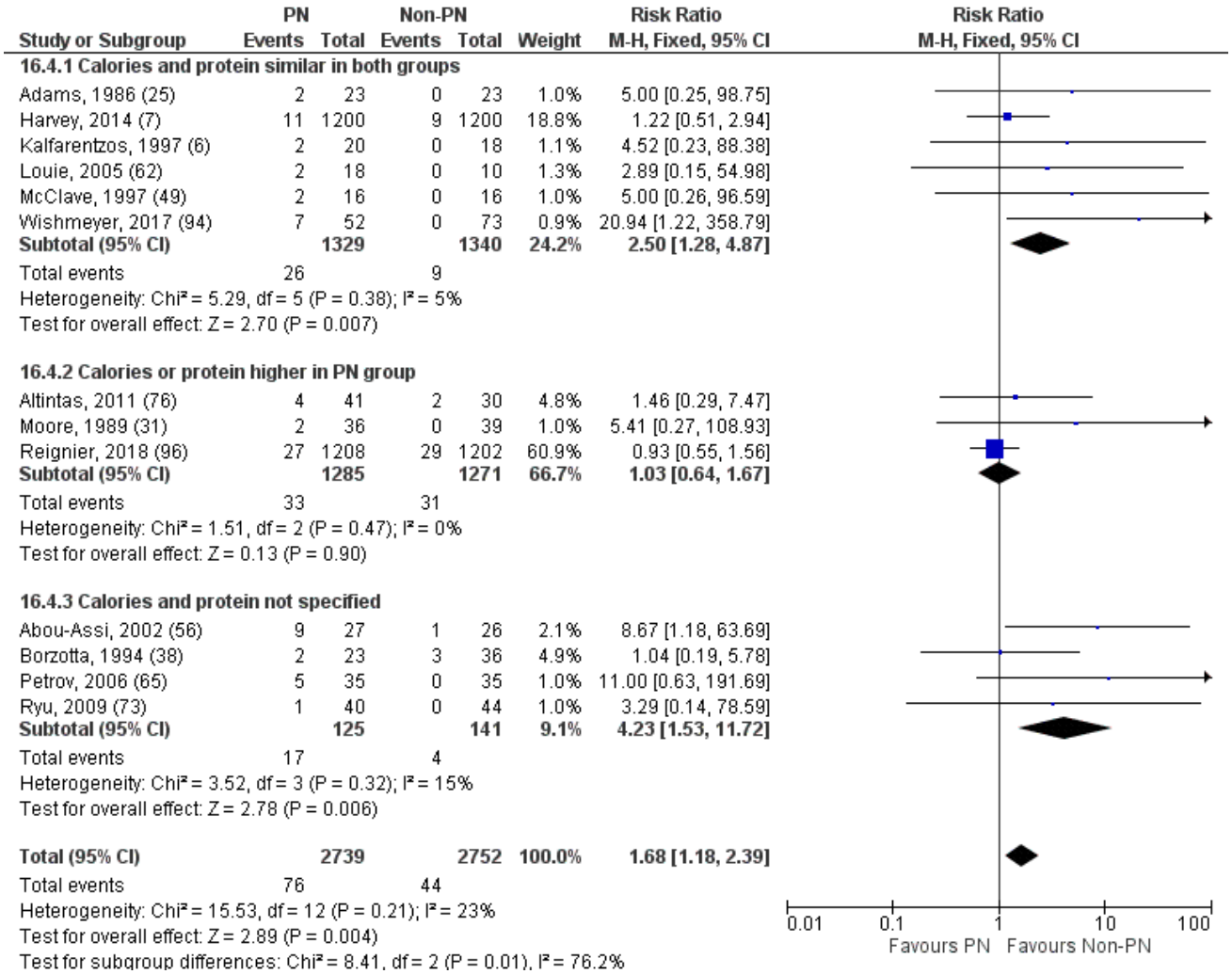


E. Catheter Infection

1) Low bias studies



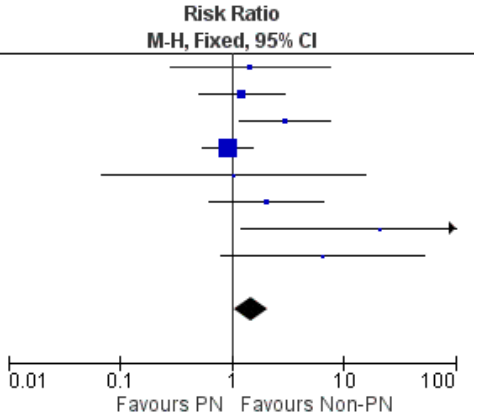
2) Severity score and glycemic control reported with calories and protein subgroup analyses



3) Excluding older studies

Study or Subgroup	PN Events	PN Total	Non-PN Events	Non-PN Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Altintas, 2011 (76)	4	41	2	30	4.7%	1.46 [0.29, 7.47]
Harvey, 2014 (7)	11	1200	9	1200	18.3%	1.22 [0.51, 2.94]
Matsushima, 2010 (74)	7	35	8	120	7.4%	3.00 [1.17, 7.69]
Reignier, 2015 (84)	27	1208	29	1202	59.2%	0.93 [0.55, 1.56]
Takesue, 2015 (85)	1	24	1	25	2.0%	1.04 [0.07, 15.73]
Terzi, 2017 (93)	3	74	20	1001	5.6%	2.03 [0.62, 6.67]
Wishmeyer, 2017 (94)	7	52	0	73	0.8%	20.94 [1.22, 358.79]
Yang, 2017 (92)	6	88	1	95	2.0%	6.48 [0.80, 52.74]
Total (95% CI)		**2722**		**3746**	**100.0%**	**1.50 [1.07, 2.12]**
Total events	66		70			

Heterogeneity: Chi² = 11.11, df = 7 (P = 0.13); I² = 37%
Test for overall effect: Z = 2.32 (P = 0.02)



15. Supplementary Table 6: Summary of findings (GRADE).

Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)
							With Non-PN	With PN	
10104 (59 RCTs)	serious [a]	not serious	not serious	not serious	none [b]	⊕⊕⊕◯ MODERATE	1270/5047 (25.2%)	1292/5057 (25.5%)	**RR 1.01** (0.95 to 1.07)
6105 (37 RCTs)	serious [a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	548/3062 (17.9%)	668/3043 (22.0%)	**RR 1.23** (1.12 to 1.36)
8297 (34 RCTs)	serious [a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	459/4157 (11.0%)	504/4140 (12.2%)	**RR 1.10** (0.98 to 1.23)
2634 (24 RCTs)	serious [a]	not serious	not serious	serious [c]	none [b]	⊕⊕◯◯ LOW	99/1348 (7.3%)	190/1286 (14.8%)	**RR 2.02** (1.63 to 2.51)
6261 (24 RCTs)	serious [a]	not serious	not serious	serious [c]	publication bias strongly suspected [d]	⊕◯◯◯ VERY LOW	44/3139 (1.4%)	76/3122 (2.4%)	**RR 2.16** (1.58 to 2.93)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. No blinding of participants and outcome assessment

b. Publication bias was detected in Egger test, but trim-and-fill computation did not change the results.

c. Confidence interval higher than 0.5

d. Publication bias was detected in Egger test

Capítulo 4

Considerações Finais

A nutrição parenteral, fruto de muitas décadas de estudo e desenvolvimento tecnológico (1), começou a ser utilizada em seres humanos no final da década de 60 (2). A partir de então, passou a ser considerada uma promissora forma de terapia nutricional para pacientes hospitalizados.

Desde o início de publicações científicas a seu respeito, elevadas taxas de complicações têm sido descritas e fez-se necessário o questionamento de qual o seu real benefício. Hoje, após diversos estudos clínicos e revisões sistemáticas é reconhecido que a terapia nutricional parenteral é associada com maiores taxas de complicações infecciosas em relação a nutrição enteral, não sendo, portanto, a forma preferencial de nutrição do paciente hospitalizado (3,4,5). Entretanto, sabe-se que os desfechos desfavoráveis em pacientes com NP são mediados por complexas interações que envolvem suas comorbidades prévias, grau de severidade da doença aguda, impacto metabólico da inutilização do trato gastrointestinal, e que vão muito além do que impacto da terapia isoladamente.

Há muito o que se estudar a respeito de NP, desde complicações específicas até a prevenção de fatores intermediários que possam mediar tais desfechos – como controle glicêmico, macro e micronutrientes e dispositivos de infusão. Nosso grupo de pesquisa focou seus esforços nessa tese em identificar complicações infecciosas – especialmente infecção de cateter venoso central – e mortalidade em pacientes em NP.

Do ponto de vista clínico, a presente tese confirmou que a NP é uma opção consolidada como terapia nutricional e que não conferiu maior risco de mortalidade de pacientes hospitalizados. No estudo de coorte retrospectivo identificou-se mortalidade próxima a 25% nos pacientes que necessitaram ser submetidos à NP no hospital. Já na revisão sistemática, ao comparar estudos randomizados com grupos semelhantes, pacientes que receberam NP não apresentaram maior mortalidade em comparação a pacientes que não

receberam nutrição parenteral. Ainda, a mesma taxa de mortalidade foi identificada na revisão sistemática, semelhante a encontrada em nosso estudo de coorte. Entretanto, a despeito de melhorias tecnológicas e de cuidados de saúde dos últimos anos, e mesmo após ajuste para possíveis mediadores de confusão conforme citado anteriormente, a nutrição parenteral seguiu significativamente associada a complicações infecciosas.

Apesar do estigma da infecção relacionada ao cateter venoso central associada a nutrição parenteral, essa não pareceu ser a principal complicação desses pacientes. Embora seja uma complicação considerável, em ambos estudos infecções de outros sítios foram mais frequentes. O estudo retrospectivo não identificou fatores específicos da solução parenteral ou aspectos relacionados ao cateter venoso central que possam mediar tal desfecho em adição ao tempo do dispositivo (considerando a ausência de fatores associados quando realizada uma análise tempo mediada utilizando tempo de cateter como referencial). O tempo de nutrição parenteral, inclusive, após controle para o tempo de cateter, não se associou a maior risco de infecção. Como análise secundária, instalar um novo cateter para a nutrição parenteral (ao invés de utilizar um cateter previamente instalado) não se associou com menores taxas de complicações infecciosas.

Já a revisão sistemática identificou maiores taxas de infecção relacionada ao cateter venoso central em pacientes que recebem nutrição parenteral, porém esse dado foi considerado uma evidência de muito baixa qualidade, conforme metodologia GRADE (foi identificado viés de publicação e ausência de diferença significativa quando selecionados apenas estudos com baixo risco de viés metodológico). Ainda assim, pacientes submetidos à NP apresentaram maiores taxas de complicações infecciosas sistêmicas, com destaque para infecções intra-abdominais.

Esta tese reforçou que do ponto de vista metodológico as revisões sistemáticas seguem como as ferramentas mais úteis para explorar e sumarizar o conhecimento disponível, mas cabe ressaltar que os achados podem diferir de acordo com a seleção do desenho dos estudos. A maior mortalidade de pacientes em NPT, por exemplo, em relação ao grupo controle, quando agrupados ensaios clínicos e estudos observacionais, não se repetiu com a

meta-análise de apenas estudos randomizados e grupos comparáveis. Já a análise de TSA representou um importante acréscimo a literatura científica vigente, uma vez que era inédita em estudos sobre NPT, e que identificou desfechos que já possuem resultados estatisticamente definitivos (mortalidade, infecção e infecção abdominal) e outros que carecem de mais dados para uma conclusão definitiva (pneumonia e infecção de cateter) na revisão sistemática apresentada.

Conhecendo a importância de terapia nutricional no impacto do paciente hospitalizado, hoje, não há espaço para discutir eticamente não oferecer alguma forma de nutrição como controle em futuros ensaios. Frente à confirmação de maiores complicações infecciosas no paciente nutridos de forma parenteral, melhorias devem ser investigadas e analisadas quanto a possibilidade de minimizar tais desfechos em pacientes sem outra possibilidade nutricional. Como perspectiva futura, a importância de analisar o impacto do uso de dieta trófica como mecanismo a diminuir translocação intestinal e consequentemente atenuar a taxa de complicações infecciosas nesses pacientes é fundamental. Além disso, é necessário avaliar a escolha de lipídeos especiais, tais como enriquecidos com ômega-3 ou novas formas de controle glicêmico (como monitorização contínua da glicemia) na prevenção de desfechos desfavoráveis em pacientes submetidos a NP.

Por fim, com os resultados dessa tese pode-se afirmar que pacientes em NP como forma de suporte nutricional possuíram elevada mortalidade, possivelmente mediada pela sua alta complexidade clínica, e não pelo suporte parenteral isoladamente. A nutrição parenteral, por outro lado, foi associada a maior taxa de complicações infecciosas sistêmicas no paciente hospitalizado, e mecanismos para mitigar tal complicação devem seguir sendo estudados. Os resultados apresentados nessa tese resumem uma importante visão sobre o conhecimento em nutrição parenteral, com importância para a prática clínica, e estimulante para o surgimento de novas pesquisas.

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