Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: A Discrete Event Simulation Model

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Original article

Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: A discrete event simulation model

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S U M M A R Y

Background & aims: A recent meta-analysis showed that supplementation of omega-3 fatty acids in parenteral nutrition (PN) regimens is associated with a statistically and clinically significant reduction in infection rate, and length of hospital stay (LOS) in medical and surgical patients admitted to the ICU and in surgical patients not admitted to the ICU. The objective of this present study was to evaluate the cost-effectiveness of the addition of omega-3 fatty acids to standard PN regimens in four European countries (Italy, France, Germany and the UK) from the healthcare provider perspective.
Methods: Using a discrete event simulation scheme, a patient-level simulation model was developed, based on outcomes from the Italian ICU patient population and published literature. Comparative efficacy data for PN regimens containing omega-3 fatty acids versus standard PN regimens was taken from the meta-analysis of published randomised clinical trials ($n = 23$ studies with a total of 1502 patients), and hospital LOS reduction was further processed in order to split the reduction in ICU stay from that in-ward stays for patients admitted to the ICU. Country-specific cost data was obtained for Italian, French, German and UK healthcare systems. Clinical outcomes included in the model were death rates, nosocomial infection rates, and ICU/hospital LOS. Probabilistic and deterministic sensitivity analyses were undertaken to test the reliability of results.
Results: PN regimens containing omega-3 fatty acids were more effective on average than standard PN both in ICU and in non-ICU patients in the four countries considered, reducing infection rates and overall LOS, and resulting in a lower total cost per patient. Overall costs for patients receiving PN regimens containing omega-3 fatty acids were between €14 144 to €19 825 per ICU patient and €5484 to €14 232 per non-ICU patient, translating into savings of between €3972 and €4897 per ICU patient and savings of between €561 and €1762 per non-ICU patient. Treatment costs were completely offset by the reduction in hospital stay costs and antibiotic costs. Sensitivity analyses confirmed the robustness of these findings.
Conclusions: These results suggest that the supplementation of PN regimens with omega-3 fatty acids would be cost effective in Italian, French, German and UK hospitals.

1. Introduction

In Italy, France, Germany and the UK, a substantial part of hospital budgets is dedicated to ICU costs, owing to the technological and personnel resources required.

Critically ill and surgical patients receive parenteral nutrition (PN) when oral or enteral nutrition is impossible, insufficient, or contra-indicated. Interest in omega-3 fatty-acid rich fish oil-

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containing lipid emulsions as part of a PN regimen has increased in recent years, with the recognition that they supply not only energy and essential fatty acids, but also very long-chain fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA), which are considered to be clinically beneficial.

A meta-analysis conducted on 23 studies – thirteen conducted in 762 patients admitted to an ICU, and ten in 740 elective surgical patients, not admitted to ICU[1] – showed that the use of fish oil-containing lipid emulsions as part of a PN regimen was associated with statistically significant and clinically relevant reductions in infection rate and of hospital and (where appropriate) ICU lengths of stay (LOS). Furthermore, supplementation with omega-3 fatty acids confers important benefits, including increased serum concentrations of alpha-tocopherol, increased EPA and DHA content of phospholipids, and enhanced leucocyte activity, together with a possible hepato-protective action (as evidenced by less elevation of ALT and AST), and a significantly greater reduction in interleukin-6 (IL-6) during the first days after initiation of the PN regimen.

The aim of the present study was to evaluate the cost-effectiveness of adding omega-3 fatty acids to standard PN regimens by merging evidence on the clinical outcomes in the Italian population with clinical effectiveness estimates from the aforementioned international meta-analysis and health resource consumption strategy in Italian hospitals. These cost-effectiveness results for Italy were then extrapolated using health resource consumption data from France, Germany and the UK in order to judge whether difference clinical practices resulted in similar pharmacoeconomic outcomes. The four national scenarios investigated represented different clinical practices for PN: in Italian and French settings, three-chamber bags are used for PN; in the UK, lipid emulsion units are used as a component of compounded PN admixtures; in the German setting, both of these systems are used (three-chamber bags or single bottles/bags).

2. Methods

For the present evaluation we used a decision analytic Discrete Event Simulation (DES) pharmacoeconomic model that includes: (i) outcomes from the Italian ICU patient population and from published literature; (ii) partially re-elaborated efficacy data from a meta-analysis of published randomised clinical trials that included 23 studies with a total of 1502 patients receiving PN supplemented with omega-3-rich fatty acids or PN standard regimens[1]; (iii) national Italian cost data; and (iv) extending these results to three further national scenarios by using French, German and UK cost data. Standard PN may be defined as those containing non-enriched lipid emulsions, namely, soybean oil, medium-chain triglycerides/long-chain triglycerides or olive/soybean oil emulsions. Please note that further details on the methods used in this study are available as a Supplementary on-line appendix.

2.1. Italian model

2.1.1. Model structure

The model was built using a DES scheme designed with the use of TreeAge Pro 2009 (TreeAge Software Inc., Williamstown, MA) software. In a DES, changes in the individuals' state are modelled over time in terms of events that occur and the consequences of those events. This DES strategy, rather than a Markov model, is used as it is particularly suitable for non-chronic situations where the timing and chronology of events are important, such as in patient groups under consideration in this study (surgical and ICU patient populations given PN).

The model simulates two treatment alternatives for patients needing PN: parenteral omega-3 enriched emulsions or standard lipid emulsions. Moreover, two patient populations are considered in this study: (i) medical and surgical patients with an ICU stay and (ii) surgical patients without an ICU stay. The following events are considered: transfers between ICU and ward, nosocomial infections, discharge from the hospital, and death, with the last two events determining the end of treatment. A simplified model structure is shown in Fig. 1(a) and (b) (for ICU and non-ICU patients, respectively). For ICU patients the publicly available *Progetto Margherita* report data are used as this is extensive and representative of the ICU population, but no such comparable source is available for non-ICU patients, therefore we used international clinical trial data for this population.[2–7]

2.1.2. Probability and outcomes

The main clinical outcomes simulated by the model are: death rate in the ICU, infection rate in the ICU, death rate in the ward, and length of hospital stay (LOS) which is divided into LOS pre-ICU, LOS in the ICU, and LOS in the ward (post-ICU for ICU patients).

The data source used for estimating the probability distributions of these outcomes in the ICU population is the 2009 edition of the *Progetto Margherita* report, an annual publication on behalf of the *Gruppo Italiano* per *la Valutazione degli Interventi in Terapia Intensiva* (GIVITI) that includes data collected in 230 Italian ICUs from a total of over 77 000 patients.[8] The GIVITI network, which covers more than half of all ICUs operating in Italy, is coordinated at the Mario Negri Institute of Pharmacology in Milan, and conducts constant monitoring of the activities and outcomes of participating ICUs. These range from medium to large in scale, university-affiliated and non-university-affiliated ICUs, and reflect the range of ICUs found in Italy. Data are collected at the patient level using standardised computer software.

The outcomes after ICU admission for this population are: (i) death in ICU (19.0%); (ii) transfer to a general ward (79.7%), or (iii) discharge from the ICU directly to home (1.3%). Among patients transferred to the general ward after ICU discharge, the mortality rate is 7.9%. In this patient population, the risk of new nosocomial infections acquired in the ICU is 11.4%. For the elective surgical population, the outcomes are: (i) death in the ward (4.76%) or (ii) discharge from ward (95.24%), and the risk of nosocomial infections is 23.0%: these represent weighted averages of the control groups included in the recent meta-analysis.[1]

The *Progetto Margherita* reports detailed information regarding hospital and ICU lengths of stay, with data given for the overall population and for subgroups of ICU/hospital outcomes. Distribution curves were fitted to these data to mathematically represent these distributions in the model, giving simulation input data for ICU patients (as shown in Table 1). For non-ICU patients, the same curve-fitting procedure was applied to data from the literature.[2–7] The times-to-events applied to the simulated patients are drawn from these fitted distributions.

2.1.3. Simulation and sensitivity analysis

In our model, the simulation takes into account the variability among individuals, while the probabilistic sensitivity analysis (PSA) allows us to consider the uncertainty of key parameters and its effect on the estimated outcomes, verifying the robustness of the numerical outcomes. This was done using a two-level Monte Carlo simulation. A deterministic sensitivity analysis (DSA) was also used. This allows us to investigate which input parameters had the greatest impact on incremental total cost and LOS. The parameters employed in the PSA and DSA analyses and their related distributions are reported in Tables 1and 2. Further details on the simulation and these sensitivity analyses is provided in the Supplementary on-line appendix.

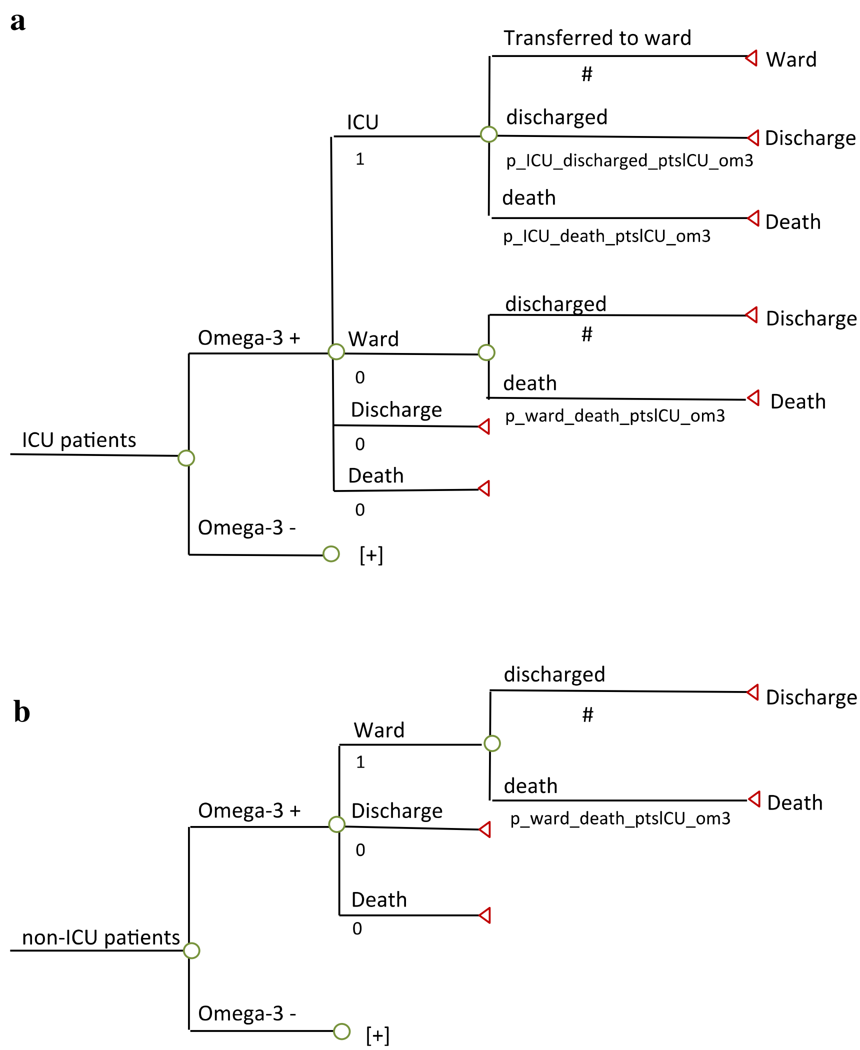


Fig. 1. a. Simplified model structure for ICU patients. b. Simplified model structure for non-ICU patients.

Table 1
a. Clinical outcomes for ICU patients in the control group used for the simulation. b. Clinical outcomes for non-ICU patients in the control group used for the simulation.

a)	
Parameter (unit)	Mean (SD)
LOS pre-ICU (days)	5.6 (9.91)
LOS ICU alive (days)	6.1 (11.40)
LOS ICU dead (days)	8.8 (16.0)
LOS post ICU alive (days)	13.7 (14.6)
Death risk in ICU	0.19
Probability ICU-ward transfer	0.80
Probability ICU-home discharge	0.01
Death risk in ward	0.08
Baseline infection rate	0.11 (0.02)
Patient bodyweight (kg)	70.13 (14.47)
Duration of PN (days)	6.13 (4.77)
b)	
Parameter (unit)	Mean (SD)
LOS (days)	17.4 (10.26)
Death risk	0.05
Baseline infection rate	0.23 (0.05)
Patient bodyweight (kg)	60.98 (10.93)
Duration of PN (days)	5.94 (1.59)

PN, parenteral nutrition; LOS, length of stay; SD, standard deviation.

2.1.4. Costs: Italy

The model includes the costs in Italy for PN, ICU and general ward stays, and cost of nosocomial infections acquired in the ICU. All costs were updated to reflect 2011 costs (Table 2).

The cost of PN is calculated for each individual as the product of the daily cost, depending on the patient weight, treatment assigned, and the duration of PN. Costs of PN are weighted according to the utilisation ratios of the two types of packaging systems for both ICU (fraction of three-chamber bags used = 0.52) and non-ICU (fraction of three-chamber bags used = 0.69) patients. For omega-3 fatty acid enriched PN, national public acquisition price for the three-chamber bag product (SmofKabiven®, manufactured by Fresenius

Table 2
Italian, French, German and UK cost parameters employed in the model (costs updated to 2011).

Cost parameters	Italy (€)	France (€)	Germany (€)	UK (£)	UK (€[a])
Daily cost ICU	1568[9]	1349[12]	1336[13]	1435–2583[14]	1765–3177
Daily cost ward	775[10]	844[15]	493[16]	266–319[17]	327–392
Cost of infection	1093[11]	3723[18]	2292–3264[19]	441[20]	542

Note: numbers in parentheses are reference numbers.
[a] Euro values are given for the UK to allow comparison with Eurozone countries (exchange rate €1.23 = £1, August 2012).

Table 3
Effect on hospital length of stay (LOS) and infection rate based on model simulations for standard (ST) and omega-3 enriched (ST + Ω3) parenteral nutrition treatments.

Mean [95% CI]	ICU patients			Non-ICU patients		
	ST + Ω3	ST	Difference	ST + Ω3	ST	Difference
LOS – total (days)	**18.59** [11.82;19.38]	**23.06** [22.11;24.15]	**−4.55** [−4.79;−4.29]	**15.70** [15.65;16.05]	**17.29** [17.20;17.60]	**−1.58** [−1.61;−1.49]
Infections/10 000 patients	**827** [477;1135]	**1086** [674;1596]	**−259** [−480;−178]	**1201** [754;1686]	**2391** [1410;3186]	**−1189** [−1511;−645]

Kabi) was considered, while public prices of available and comparable three-chamber bags were considered for standard PN.

For each possible patient weight the daily cost for each brand has been calculated by choosing the smallest sufficient content, on a basis of a lipid intake of 1.3 g fat/kg BW/day. The daily cost for each patient weight was then calculated by weighting the product prices according to their national market shares. Individual patient weights in the model are sampled from distributions reflecting the *Progetto Margherita* population for ICU patients, and the populations enrolled in the clinical trials included in our earlier meta-analysis for patients not admitted to an ICU.

In order to estimate the average daily cost of Italian ICUs, we relied on the results of prospective case-control studies. For Italy, the results by Tarricone[9] yield a value of €1498 (2011 value €1568), after subtracting the costs for surgical procedures and for extra antibiotics in their sepsis patients, considered separately for patients developing nosocomial infections in the simulation.

The average daily cost of a hospital ward was taken from the 2005 report of the National Agency for Regional Health Services[10] for Italy. This estimate includes fixed overhead costs of heating, lighting, laundry, provision of food for patients, and average costs for medicines and staff, actualised to 2011 values of €775.

Nosocomial infections acquired in the ICU significantly increase overall hospital costs, mainly from the prolongation of hospital LOS. Since the effect of omega-3 fatty acid supplementation on the infection rate is already modelled in terms of the reduction of the average LOS, we chose not to include an extra effect on the LOS resulting from the reduced infection rate in order to avoid double counting. Thus, we limited the cost of any new infection to that of the additional antibiotics needed. We employed the average infection cost reported by Orsi et al.[11] in Italy for the treatment of ICU-emergent bloodstream infections, actualised to a 2011 value of €1093.

2.2. Extension of the model to France, Germany and the UK

The model was extended to encompass the costs for each of the three other markets of interest (France, Germany and UK) for PN, ICU and general ward stays, and cost of nosocomial infections acquired in the ICU.[12–20] All costs were updated to reflect 2011 costs (Table 2). Further details on these costs are outlined in the full methods section within the Supplementary on-line appendix.

3. Results

3.1. Italy

Table 3 represents the effect on hospital LOS and infection rate based on model simulations for standard and omega-3 enriched PN. These base-case results were obtained by calculating outcomes of interest for 10 000 simulated patients. Omega-3 fatty acid-containing lipid emulsions are expected to be more effective than standard PN, as they would prevent almost one quarter (259 of 1086) of infections in ICU patients and one-half (1189 of 2391) of infections in non-ICU patients and reduce overall LOS.

Table 4 shows the base-case scenario for Italy for costs, based on model simulations for standard and omega-3 enriched PN. Total costs associated with a fish oil-based PN regimen are, on average, lower than with standard PN with a mean cost saving per ICU and non-ICU patient, respectively, of about €4700 and €1000 in Italy (Table 4). These findings indicate that the extra cost for omega-3 fatty acid-containing PN is completely offset by the reduction in hospital stay costs, and to a lesser extent by lower antibiotic costs for the treatment of emergent infections. Indeed, inclusion of omega-3 fatty acids in PN is expected to dominate standard PN regimens on average, as it is associated with better clinical and economic outcomes observed in 88% of ICU patients and in 68% of non-ICU patients in Italy.

3.2. France, Germany and the UK

Base-case results for the effect on hospital LOS and infection rates (based on model simulations for standard and omega-3 enriched PN) are the same as those found in the previous section (see Table 3).

Total costs associated to a fish oil-based PN regimen are, on average, lower than with standard PN, with a mean cost saving per ICU and non-ICU patient, respectively, of about (i) €4900 and €1800 in France (ii); €4000 and €1300 in Germany; and (iii) £4100 and £500 in the UK (Table 5). These findings indicate that the extra

Table 4
Costs based on model simulations for standard (ST) and omega-3 enriched (ST + Ω3) parenteral nutrition treatments: results for Italy.

Mean [95% CI]	ICU patients			Non-ICU patients		
	ST + Ω3	ST	Difference	ST + Ω3	ST	Difference
Italy (€)						
Total	**19 825** [14 847;25 191]	**24 504** [18 266;31 265]	**−4679** [−6121;−3372]	**13 595** [8832;18 663]	**14 619** [9383;20 197]	**−1025** [−1540;−546]
ICU	**7475** [4698;10 607]	**10 166** [6389;14 415]	**−2691** [−3812;−1688]	NA	NA	NA
Ward (pre-ICU)	**4318** [2703;6076]	**4318** [2703;6076]	**0** [0;0]	NA	NA	NA
Ward	**6336** [3799;8912]	**8531** [5102;11 972]	**−2195** [−3064;−1300]	**12 171** [7560;17 379]	**13 399** [8299;19 086]	**−1228** [−1709;−737]
Infection	**90** [37;139]	**119** [52;196]	**−28** [−58;−14]	**131**[59;212]	**261** [110;401]	**−130** [−190;−50]
Treatment	**1605** [1442;1627]	**1370** [1232;1394]	**235** [203;240]	**1292** [1132;1152]	**959** [836;848]	**333** [293;307]
ICER (€/LOS day)			*Dominant*			*Dominant*

ICER, incremental cost-effectiveness ratio (Ω3 *vs* ST); LOS, length of stay.
Note: death rates per 10 000 patients are 2509 (ICU patients) and 511 (non-ICU patients), regardless of treatment in all of the base-case scenarios.

Table 5
Costs based on model simulations for standard (ST) and omega-3 enriched (ST + Ω3) parenteral nutrition treatments: results for France, Germany and the UK.

Mean [95% CI]	ICU patients			Non-ICU patients		
	ST + Ω3	ST	Difference	ST + Ω3	ST	Difference
France (€)						
Total	**18 964** [13 950;24 468]	**23 861** [17 630;30 713]	**−4897** [−6287;−3637]	**14 232** [9197;19 947]	**15 994** [10 357;22 228]	**−1762** [−2319;−1123]
ICU	**6427** [4039;9120]	**8741** [5493;12 394]	**−2314** [−3277;−1451]	NA	NA	NA
Ward (pre-ICU)	**4705** [2945;6620]	**4705** [2945;6620]	**0** [0;0]	NA	NA	NA
Ward	**6903** [4139;9709]	**9295** [5559;13 044]	**−2392** [−3339;−1416]	**13 261**[8237;18 935]	**14 599** [9042;20 795]	**−1338** [−1862;−803]
Infection	**308** [125;475]	**404** [179;667]	**−96** [−198;−47]	**447** [201;722]	**890** [374;1366]	**−443** [−647;−170]
Treatment	**621** [586;659]	**716** [678;764]	**−96** [−107;−89]	**524** [520;529]	**505** [501;508]	**19** [18,22]
ICER (€/LOS day)			*Dominant*			*Dominant*
Germany (€)						
Total	**14 144** [10 837;17 893]	**18 117** [13 868;22 943]	**−3972** [−5084;−2996]	**8841** [5842;12 078]	**10 176** [6601;13 931]	**−1335** [−2116;−498]
ICU	**6369** [3944;9120]	**8662** [5360;12 393]	**−2293** [−3276;−1413]	NA	NA	NA
Ward (pre-ICU)	**2748** [1760;3798]	**2748** [1760;3798]	**0** [0;0]	NA	NA	NA
Ward	**4031** [2508;5592]	**5428** [3369;7508]	**−1397** [−1918;−859]	**7744** [4839;10 840]	**8525** [5314;11 903]	**−781** [−1064;−474]
Infection	**209** [−83;507]	**274** [−117;713]	**−65** [−209;36]	**392** [−423;1257]	**780** [−800;2376]	**−388** [−1121;378]
Treatment	**787** [748;837]	**1005** [955;1072]	**−217** [−236;−205]	**704** [698;709]	**870** [865;876]	**−166** [−169;−164]
ICER (€/LOS day)			*Dominant*			*Dominant*
UK (£)						
Total	**13 333** [11 124;16 098]	**17 463** [14 458;21 193]	**−4130** [−5103;−3326]	**4674** [4336;5071]	**5152** [4764;5571]	**−478** [−510;−418]
ICU	**9208** [7018;11 987]	**12 522** [9546;16 284]	**−3315** [−4302;−2522]	NA	NA	NA
Ward (pre-ICU)	**1593** [1457;1737]	**1593** [1457;1737]	**0** [0;0]	NA	NA	NA
Ward	**2338** [2025;2606]	**3148** [2717;3500]	**−810** [−898;−689]	**4491** [4152;4888]	**4944** [4561;5367]	**−453** [−482;−406]
Infection	**37** [15;58]	**48** [21;82]	**−11** [−25;−6]	**53** [23;84]	**106** [44;159]	**−53** [−75;−20]
Treatment	**158** [151;169]	**152** [145;163]	**6** [5,7]	**130** [129;130]	**102** [101;103]	**28** [27;28]
ICER (£/LOS day)			*Dominant*			*Dominant*
UK (€)						
Total	**15 646** [13 054;18 890]	**20 492** [16 966;24 869]	**−4846** [−5988;−3903]	**5484** [5088;5950]	**6045** [5590;6537]	**−561** [−599;−490]
ICU	**10 805** [8236;14 066]	**14 694** [11 201;19 109]	**−3890** [−5049;−2959]	NA	NA	NA
Ward (pre-ICU)	**1870** [1710;2039]	**1870** [1710;2039]	***0*** [0;0]	NA	NA	NA
Ward	**2743** [2376;3058]	**3694** [3189;4107]	**−950** [−1054;−808]	**5270** [4872;5736]	**5802** [5353;6298]	**−532** [−566;−476]
Infection	**43** [17;68]	**56** [24;96]	**−13** [−29;−7]	**62** [27;99]	**124** [51;186]	**−62** [−88;−24]
Treatment	**186** [177;198]	**178** [170;191]	**7 [6,9]**	**152** [151;153]	**120** [119;120]	**32** [32;33]
ICER (€/LOS day)			*Dominant*			*Dominant*

ICER, incremental cost-effectiveness ratio (Ω3 *vs* ST); LOS, length of stay.
Note: death rates per 10 000 patients are 2509 (ICU patients) and 511 (non-ICU patients), regardless of treatment in all of the base-case scenarios.

cost for omega-3 fatty acid-containing PN is completely offset by the reduction in hospital stay costs, and to a lesser extent by lower antibiotic costs for the treatment of emergent infections. Indeed, inclusion of omega-3 fatty acids in PN is expected to dominate standard PN regimens on average, as it is associated with better clinical and economic outcomes observed in 88–90% of ICU patients and in 71–73% of non-ICU patients in France, Germany, and the UK.

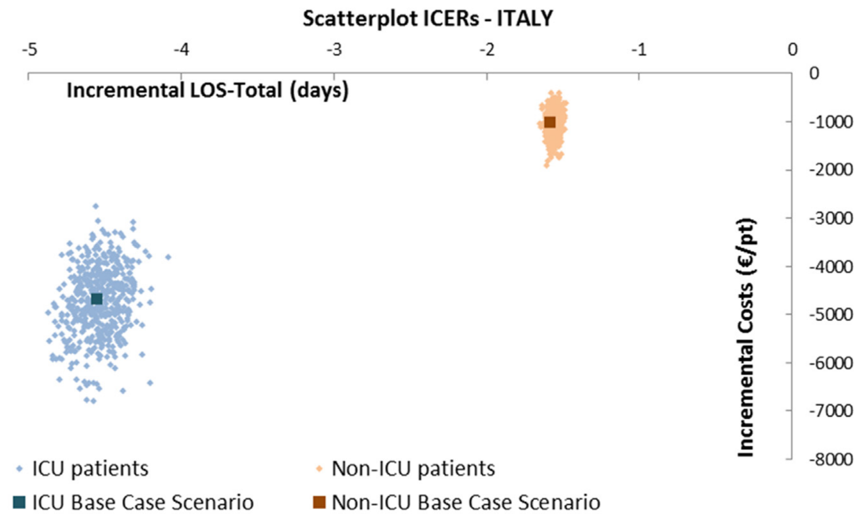
3.3. Sensitivity analysis

The results of the PSA show that mean effectiveness and cost estimates differ slightly from those resulting from the base-case analysis, but the conclusions are consistent: total costs associated with standard PN supplemented with omega-3 fatty acids are expected to be lower, while patient outcomes are anticipated to be improved, as compared to standard PN. Consequently, omega-3 supplemented PN is expected to be more cost-effective than standard PN. In particular, it was observed that in all PSA simulations omega-3 enriched PN was associated with clinical and economic superiority, as depicted on the cost-effectiveness plane as a dot in the ‘south-west’ quadrant. These results for Italy are shown in Fig. 2, but very similar results were also found for France, Germany and the UK (not shown). These results indicate the reliability of the main conclusion regarding clinical and economic superiority. A careful observation of the scatterplot (Fig. 2) also reveals a high degree of correlation between cost and LOS savings, which is not surprising given that hospital stay is one of the major drivers of costs.

DSA estimations confirm that the cost difference between the two treatments is mostly influenced by daily ward costs and LOS reduction in both ICU and non-ICU patients (Figs. 3 and 4, respectively, for Italy). Note that very similar results were obtained for other countries (not shown). Weight and lipid dose show a peculiar effect, as variations in both directions result in reduced cost savings with omega-3 supplementation. This depends on the *difference* between PN daily cost in omega-3 and standard treatment; it is lower in the base-case than in cases of weight or dose increases and decreases. None of the variations that we tested changes the main conclusion of the study: that on average, the addition of omega-3 fatty acids to the nutrition regimen is a cost-saving strategy. (Although for ICU patients undergoing surgery and not admitted to the ICU, dominance was lost when the upper limit of the credibility interval for the relative ward LOS – which was above 1 – was tested.)

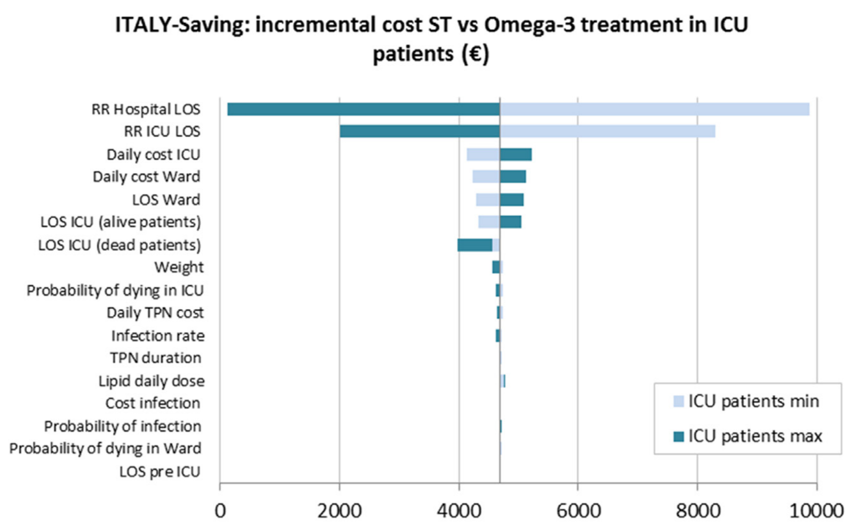
4. Discussion and conclusions

In conclusion, the results of the present model indicate that the addition of omega-3 fatty acids to standard PN regimens has the potential to significantly improve outcomes in both ICU and non-ICU patients, while also leading to cost savings in Italian, French, German, and UK hospitals. The magnitude of the benefits for adding omega-3 fatty acids to standard PN regimens is also similar to those reported in the literature. For example, we have reported reductions in infection rates of approximately one quarter (ICU infections) and one half (non-ICU infections). In Pradelli et al.[1] ICU infections were reduced by 29% and non-ICU infections by 47% (all infections: RR 0.61; 95% CI 0.45–0.84; $p < 0.05$). Likewise the meta-analysis of Chen et al.[21] concerning fish-oil enriched parenteral nutrition, showed a large and significant reduction in postoperative



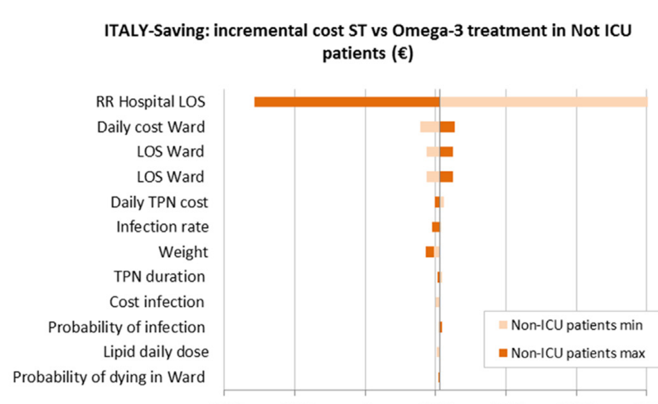
LOS, length of stay.

Fig. 2. Scatterplot of 1000 incremental cost-effective ratios (ICERs) *(x^2)* estimates in the probabilistic sensitivity analysis (PSA) for Italy.



LOS, length of stay; TPN, total parenteral nutrition; RR, relative risk; ST, standard treatment.

Fig. 3. Tornado plots representing the sensitivity of cost savings with omega-3 supplementation to variation in key parameters: ICU patients in Italy.



LOS, length of stay; TPN, total parenteral nutrition; RR, relative risk; ST, standard treatment.

Fig. 4. Tornado plots representing the sensitivity of cost savings with omega-3 supplementation to variation in key parameters: non-ICU patients in Italy.

infection rates with supplementation (odds ratio 0.56; 95% CI 0.32–0.98; $p = 0.04$).

A possible limitation of the model is the heterogeneity in the patient populations in the clinical studies included in the meta-analysis. However, the patients, although admitted with a variety of diagnoses, share the common pathophysiological feature of imbalanced lipid mediators that favour a pro-inflammatory state, which is ameliorated by omega-3 fatty acids. Other limitations of the present study are inherent to the modelling approach in general, in particular to the need for combining different data sources into a single logical construct. The use of modelling in economic evaluations is accepted as an unavoidable fact of life.[22] In essence, models can represent the complexity of the real world in a more simple and comprehensible form, and are often used in health economic evaluations where the relevant clinical trials have not been conducted or did not include economic data capture. In these cases decision analytic models are used to synthesise the best available data.[22] Decision models are particularly useful for combining or linking data from different research areas and sources and/or transferring or extrapolating results from one time, place, population, or setting, to another.[23] Modelling needs to used by healthcare decision-makers as waiting until perfect information is available is, in most cases, not a realistic option, and so costs and consequences of a particular healthcare strategy need to be based on available data.[23]

However, models can only be reliable if they are based on good-quality evidence. In the current model, we used a mixture of sources, including meta-analysis data. The use of meta-analysis data is standard within pharmacoeconomic analyses, but potential drawbacks are that meta-analyses involve making judgements on which studies to include and are generally only reliable if several medium or large trials are included. Nevertheless, such analyses are an opportunity to draw together all available and suitable data, to increase sample size and thus the power to detect effects of interest.

The overall value of the saving is quite consistent among the settings analysed, although the contribution of the single cost items is different, reflecting different hospital models across these European countries. This observation, coupled with the robustness of model results in the sensitivity analyses (conducted to assess the effect of parameter uncertainty), indicate our results may be generalisable to many different settings not specifically addressed in this study.

In conclusion, the results of this modelling study strongly suggest that the addition of omega-3 fatty acids to standard PN is a clinically and economically attractive strategy, representing a 'win–win' scenario for both patients and healthcare providers. This is because supplementation of lipid emulsions with omega-3 fatty acids reduces infection rates and length of hospital stay in ICU and in non-ICU patients receiving PN. As a consequence, supplementary treatment costs are completely offset by the reduction in the cost of hospital stay and antibiotics. As such, the results of the model show that supplementation of lipid emulsions with omega-3 fatty acids is highly likely to lead to cost savings in Italian, French, German, and UK hospitals.

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Statement of authorship

LP conceived the study and drafted the manuscript. ME conceived the study and helped in drafting the manuscript. MP coded the model and performed statistical analyses. KM participated in the design of the study, reviewed the literature and helped to draft the manuscript. MM participated in the design of the study, reviewed the literature and helped to draft the manuscript. AH participated in the design of the study, reviewed the literature and helped to draft the manuscript. EF-S participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of interest

LP is co-owner and employee of AdRes, which has received project funding from Fresenius Kabi. MP is employee of AdRes, which has received project funding from Fresenius Kabi. ME has no competing interests to declare. MM has received speaker honoraria from Baxter, B. Braun and Fresenius Kabi. KM received fees for product-neutral lectures and compensation for travel costs from Abbott, Baxter, B. Braun, Fresenius Kabi, MSD, Nestlé, and Pfizer. ARH has received speaker honoraria and project funding from B. Braun, Melsungen, Germany and from Fresenius Kabi, Bad Homburg, Germany. EF-S is an employee of Fresenius Kabi.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2013.11.016.

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