Economic burden of hospital malnutrition and the cost–benefit of supplemental parenteral nutrition in critically ill patients in Latin America

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Aim: Disease-related malnutrition (DRM) is a prevalent condition that significantly increases the risk of adverse outcomes in hospitalized patients, particularly those with critical illness. Limited data is available on the economic burden of DRM and the cost–benefit of nutrition therapy in high-risk populations in Latin America. The aims of the present study were to estimate the economic burden of DRM and evaluate the cost–benefit of supplemental parenteral nutrition (SPN) in critically ill patients who fail to receive adequate nutrient intake from enteral nutrition (EN) in Latin America.

Methods: Country-specific cost and prevalence data from eight Latin American countries and clinical data from studies evaluating outcomes in patients with DRM were used to estimate the costs associated with DRM in public hospitals. A deterministic decision model based on clinical outcomes from a randomized controlled study and country-specific cost data were developed to examine the cost–benefit of administering SPN to critically ill adults who fail to reach >60% of the calculated energy target with EN.

Results: The estimated annual economic burden of DRM in public hospitals in Latin America is $10.19 billion (range, $8.44 billion–$11.72 billion). Critically ill patients account for a disproportionate share of the costs, with a 6.5-fold higher average cost per patient compared with those in the ward ($5488.35 vs. $839.76). Model-derived estimates for clinical outcomes and resource utilization showed that administration of SPN to critically ill patients who fail to receive the targeted energy delivery with EN would result in an annual cost reduction of $10.2 million compared with continued administration of EN alone.

Limitations: The cost calculation was limited to the average daily cost of stay and antibiotic use. The costs associated with other common complications of DRM, such as prolonged duration of mechanical ventilation or more frequent readmission, are unknown.

Conclusions: DRM imposes a substantial economic burden on Latin American countries, with critically ill patients accounting for a disproportionate share of costs. Cost–benefit analysis suggests that both improved clinical outcomes and significant cost savings can be achieved through the adoption of SPN as a therapeutic strategy in critically ill patients who fail to receive adequate nutrient intake from EN.

Introduction

Disease-related malnutrition (DRM) is a highly prevalent condition and a major public health issue that imposes a substantial economic burden on hospitals, payers, and society. DRM is associated with significant adverse clinical consequences, including increased risk of infectious and non-infectious complications, increased length of hospitalization, more frequent readmission, and increased mortality. As a consequence, malnourished patients consume an increased proportion of healthcare resources compared with those who are well nourished.

Studies evaluating direct medical costs associated with DRM have reported estimated annual costs of $9.5–$15.5 billion in the United States and more than €31 billion in Europe. When mortality and lost quality-adjusted life years are considered, DRM is associated with an estimated annual financial burden of $157 billion in the United States, €305 billion in Europe and $66 billion in China. Supplemental parenteral nutrition (SPN) has been shown to significantly improve nutrition balance and reduce the risk of infection in critically ill patients who fail to achieve sufficient intake via enteral nutrition (EN), and pharmacoeconomic analysis has shown that the favorable effect of SPN on clinical outcomes is associated with a meaningful cost benefit compared with the continued administration of EN alone.

A recent systematic review of studies evaluating the prevalence of malnutrition in Latin American hospitals reported that 40–60% of patients exhibit evidence of malnutrition at the time of admission, with data from several...
studies showing an increase in prevalence with increasing duration of hospitalization\textsuperscript{25}. A subsequent study assessing clinical nutrition practices in intensive care units (ICUs) in eight Latin American countries showed that 74\% of critically ill adults who were receiving nutrition therapy were classified as moderately to severely malnourished according to the Subjective Global Assessment (SGA). Nutrition intake failed to reach the cumulative target in nearly 40\% of all patients, resulting in a mean cumulative caloric deficit of more than 3200 kcal during a maximum observation period of 5 days\textsuperscript{26}. Only 10\% of patients received SPN, suggesting an opportunity to improve clinical outcomes and reduce costs through more effective use of SPN in critically ill patients who fail to receive adequate intake from EN.

While the prevalence and clinical consequences of DRM in hospitalized patients in Latin America have been previously described, limited data is available on the magnitude of the economic burden and the economic effect of various interventions such as the administration of SPN to critically ill patients for whom EN alone is insufficient to meet nutritional needs. Therefore, the dual aims of the present study were to (a) estimate the economic burden of DRM in hospitalized patients in Latin America, with a special focus on those with critical illness, and (b) evaluate the economic impact of individually optimized nutrition provision with SPN in critically ill patients.

Methods

Economic burden of disease-related malnutrition

The effect of DRM on hospital costs was evaluated from the perspective of public hospitals in eight Latin American countries (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Panama and Peru). Based on evidence from prior studies\textsuperscript{5,13,14,27,28}, increased length of stay (LOS) and increased antibiotic use due to healthcare-associated infection (HAI) were selected as sources of increased cost among malnourished patients. Costs were calculated separately for the ward and the ICU to account for differences in DRM prevalence, HAI incidence, average LOS and average daily cost of stay.

Calculation of cost due to increased length of stay

The following formula was developed to calculate the additional cost attributable to the increase in LOS in patients with DRM:

$$\text{Additional cost} = \frac{p \times LOS_a}{(p \times LOS_a) + 1} \times n \times LOS_a \times c_d$$

where $p =$ prevalence of DRM on admission; $LOS_a =$ increase in LOS due to DRM (expressed as a relative percentage); $LOS_a =$ average LOS, $n =$ number of hospitalized patients per year; and $c_d =$ average daily cost.

Country-specific values for each variable are summarized in Table 1; data sources for each variable are summarized by country in Supplemental File 1. The prevalence of DRM among patients hospitalized in the ward was obtained from the published literature\textsuperscript{20,29–32}. For countries in which DRM prevalence was not measured at the time of admission\textsuperscript{29}, the reported prevalence was converted according to the following formula:

$$\text{DRM prevalence on admission} = \frac{DRM_{prev}}{(DRM_{prev} + [1 + LOS]) \times (1 - DRM_{prev})}$$

where $DRM_{prev} =$ reported prevalence of DRM and $LOS =$ relative increase in LOS due to DRM.

Population size, annual number of hospitalized patients and average LOS ($LOS_a$) in the ward were obtained from published literature, official records and public databases for the respective countries\textsuperscript{33–45}. The increase in LOS attributable to DRM ($LOS_r$) was determined based on the calculated mean increase in LOS reported in the two Latin American studies evaluating LOS in patients with DRM (84.5\%)\textsuperscript{13,14}. Costs were also calculated using the reported LOS increases of 64\% and 105\% individually to establish upper and lower boundaries for the estimate.

The average daily cost of stay in the ward was available from official records for two countries (Argentina and Mexico)\textsuperscript{46,47}. The estimated daily cost of hospitalization excluding drugs and diagnostic tests was available from the WHO-CHOICE database for all countries\textsuperscript{48}. To account for excluded costs, the average daily cost of stay in countries other than Argentina and Mexico was calculated by multiplying the country-specific estimated daily cost of hospitalization from the WHO-CHOICE database by the average relative difference between the average daily cost from the official records and the WHO-CHOICE estimates for Argentina and Mexico.

The total number of ICU patients per year was derived from the number of public ICU beds obtained from published sources in four countries\textsuperscript{49–52}. The number of ICU beds was multiplied by the country-specific mean LOS and an assumed occupancy rate of 80\%. For countries in which there was no published data, the annual number of ICU patients was derived based on the mean relative proportions of ICU and ward patients in the countries for which data was available. The estimated prevalence of DRM among ICU patients was based on published data\textsuperscript{53}. The average LOS in the ICU ($LOS_{ICU}$) was obtained from either the published literature or public databases for five countries (Argentina, Brazil, Colombia, Ecuador and Mexico)\textsuperscript{52,44,45–56}; for the remaining countries (Chile, Panama and Peru), the mean LOS from the five countries with available data was used. The increased LOS attributable to DRM in ICU patients was determined using the method described for ward patients.

The average daily cost of stay in the ICU was obtained from official records for Argentina and Mexico\textsuperscript{46,47}. For countries in which there was no available data, the average daily cost of stay was determined by multiplying the calculated cost of stay in the ward by the average relative difference in the cost of stay in the ward and the ICU in Argentina and Mexico.

Calculation of cost due to increased antibiotic use

Costs associated with the increase in antibiotic use due to HAI in patients with DRM were calculated using the following formula:

$$n \times p \times (HAIDRM - HAINoDRM) \times C_a$$
A series of deterministic one-way sensitivity analyses was performed to assess the sensitivity of the country-specific cost estimates to the underlying assumptions by varying the values for each model parameter by ±20%.

### Cost–benefit analysis: supplemental parenteral nutrition in intensive care unit patients with caloric deficits

**Analytic model and source data**

The cost–benefit analysis was conducted from the perspective of public hospitals in Latin America. A deterministic pharmacoeconomic decision model was used to examine the cost benefit ratio of administering SPN to critically ill adults who fail to reach ≥60% of the calculated energy target with EN.

The model integrated clinical data from the Swiss SPN study23,24 and epidemiological data from the Latin America Screening Day study26 with population and cost data derived from local sources 46–48,64,66–71 to simulate clinical outcomes and resource utilization.

The Swiss SPN study was a randomized controlled study evaluating the effect of EN plus SPN compared with EN alone on days 4–8 in critically ill adults (N = 305) who failed to achieve ≥60% of the targeted energy delivery with EN.23 A subsequent analysis of data from the Swiss SPN study showed that each 1000 kcal decrease in cumulative energy deficit was associated with a 10% reduction in the risk of nosocomial infection.24 Based on the observed mean reduction in cumulative energy deficit of 2130 kcal in patients

### Table 1. Country-specific values for the variables included in the cost analysis.

| Country     | Argentina | Brazil | Chile | Colombia | Ecuador | Mexico | Panama | Peru | Total |
|-------------|-----------|--------|-------|----------|---------|--------|--------|------|-------|
| Ward        | 1,673,363 | 11,155,473 | 1,005,076 | 1,654,318 | 704,214 | 6,435,684 | 146,953 | 694,310 | 23,469,391 |
| ICU         | 35,353    | 207,207 | 21,234 | 12,851   | 31,344  | 92,690  | 3,105  | 19,193 | 423,247 |
| Average LOS, days | Ward 5.9 | 4.5 | 6.6 | 4.9 | 4.67 | 4.4 | 5.0 | 4.9 | 5.1 |
|             | ICU 7.15 | 11.3 | 7.6 | 6.92 | 5.32 | 7.4 | 7.6 | 7.6 | 7.6 |
| DRM prevalence, % | Ward 35.8 | 45.7 | 24.2 | 63.0 | 31.2 | 49.1 | 27.0 | 35.2 | 38.9 |
|             | ICU 54.0 | 54.0 | 54.0 | 54.0 | 54.0 | 54.0 | 54.0 | 54.0 | 54.0 |
| Increase in LOS due to DRM, %13,14 | 84.5 | 84.5 | 84.5 | 84.5 | 84.5 | 84.5 | 84.5 | 84.5 | 84.5 |
| HAI incidence, % | Ward 9.6 | 14.0 | 5.9 | 4.2 | 8.8 | 12.9 | 5.0 | 3.9 | 8.0 |
|             | ICU 25.9 | 11.0 | 15.9 | 11.2 | 23.0 | 14.1 | 27.7 | 17.7 |
| Increase in HAI due to DRM, %16 | 92.1 | 92.1 | 92.1 | 92.1 | 92.1 | 92.1 | 92.1 | 92.1 |
| Cost/day, $  | Ward 213.67 | 246.14 | 358.88 | 148.99 | 168.56 | 392.94 | 253.75 | 168.93 | 243.98 |
|             | ICU 463.66 | 872.56 | 1272.21 | 528.16 | 597.55 | 1933.22 | 899.54 | 589.84 | 895.72 |
| Antibiotic therapy cost per episode of HAI, $ | 1245.00 | 698.90 | 352.90 | 358.80 | 939.60 | 914.00 | 1236.90 | 525.80 | 783.99 |

**Abbreviations.** DRM, disease-related malnutrition; HAI, healthcare-associated infection; ICU, intensive care unit; LOS, length of stay.

where n = number of patients per year; p = prevalence of DRM; HAI_{DRM} = infection risk, DRM; HAI_{NO DRM} = infection risk, no DRM; C2 = average cost of antibiotic therapy per infectious episode.

HAI rates were obtained from the published literature and official records from the participating countries (Supplemental File 1)46,57–65. For Mexico, HAI prevalence data was converted to incidence estimates using the method described above for the conversion of the reported DRM prevalence to the estimated prevalence at the time admission. The increase in HAI among malnourished patients was based on the observed increase in the incidence of infection in the study by Correia and Waitzberg4. The average cost of antibiotic therapy per infectious episode was obtained from the published literature and converted to US dollars and adjusted to 2017 values.64,66–71

### Sensitivity analysis – economic burden

A series of deterministic one-way sensitivity analyses was performed to assess the sensitivity of the country-specific cost estimates to the underlying assumptions by varying the values for each model parameter by ±20%.
receiving SPN, an odds ratio of 0.8 was used to determine the occurrence of HAI in the two groups in the cost–benefit model.

The Latin America Screening Day study was a multinational observational study evaluating clinical nutrition practices in critically ill adults (N=1053) in eight Latin American countries\(^{26}\). Nutrition status, type and volume of nutrition therapy, and caloric balance were assessed during a maximum observation period of 5 days.

**Clinical and epidemiological variables**

A schematic representation of the cost–benefit model is depicted in Figure 1. Country-specific values for the annual number of ICU patients and the proportion receiving EN are summarized in Table 2. Clinical outcomes in the model included new onset of HAI and LOS in the ICU and ward. The first step in the model was the determination of the nutritional adequacy of EN, defined as ≥60% of the calculated energy target. The number of patients achieving <60% of the energy target with EN was determined for each country by multiplying the annual number of ICU patients by the proportion of patients who received EN alone in the Screening Day study\(^{24}\) and then multiplying the result by the proportion of patients achieving <60% of the energy target with EN in the Screening Day study (unpublished data).

The subsequent step in the model was the decision to either continue nutrition therapy with EN alone or initiate SPN. The occurrence of HAI was then determined in each treatment group based on the observed odds ratio for new occurrence of nosocomial infection in the Swiss study\(^{24}\) and the country-specific HAI incidence as follows:

\[
\text{Odds of } HAI_{(EN)} = 0.8 \times \left( \frac{HAI \text{ incidence}}{1 - HAI \text{ incidence}} \right)
\]

\[
\text{Odds of } HAI_{(SPN)} = \frac{\text{Odds of } HAI_{(EN)}}{1 + \text{Odds of } HAI_{(SPN)}}
\]

**Resource utilization and associated costs**

In the final step in the model, resource utilization was determined according to infection status based on the differences in LOS and the use of antibiotic therapy. For LOS, values were assigned based on the mean difference in LOS between infected and non-infected patients in the Swiss SPN study\(^{24}\). The average daily costs for the ward and the ICU and the average cost of antibiotic therapy per episode of HAI were obtained from country-specific sources as described above\(^{46-48,64,66-71}\). The daily cost of EN was calculated based on the reported mean caloric intake in each country in the Screening Day study\(^{26}\) and the mean cost of the corresponding dose of available EN products. The daily cost of SPN was calculated using the weighted mean cost of the smallest bag size for the available PN products and an assumed duration of nutrition therapy of 5 days. The latter was selected to correspond with the duration of nutrition therapy in the Swiss SPN study.

![Figure 1. Deterministic decision model. Abbreviations. EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay; SPN, supplemental parenteral nutrition.](image)

**Table 2. Country-specific ICU patient population estimates.**

| Country          | ICU patients/year, n | Receive EN, % | Receive EN, n | <60% energy target, % |
|------------------|----------------------|--------------|---------------|-----------------------|
| Argentina        | 35,353\(^{a}\)       | 70.0         | 26,514        | 4.0                   |
| Brazil           | 207,207\(^{b}\)      | 75.0         | 168,873       | 21.0                  |
| Chile            | 21,234\(^{a}\)       | 76.0         | 12,992        | 30.0                  |
| Colombia         | 12,851\(^{b}\)       | 72.0         | 9,677         | 18.0                  |
| Ecuador          | 31,344\(^{b}\)       | 64.0         | 20,342        | 13.0                  |
| Mexico           | 92,690\(^{b}\)       | 67.0         | 63,420        | 4.0\(^{d}\)           |
| Panama           | 3105\(^{a}\)         | 72.0         | 2040          | 18.0                  |
| Peru             | 19,193\(^{a}\)       | 82.0         | 14,602        | 16.3                  |
| Total            | 423,247              | 75.2         | 318,460       |                       |

\(^{a}\)Calculated by multiplying the number of hospital patients by the mean proportion of ICU patients among hospitalized patients in the countries for which the number of public ICU beds was available.

\(^{b}\)Calculated based on reported number of public ICU beds, an assumed average occupancy rate of 80%, and the country-specific mean length of stay in the ICU.

\(^{c}\)Data on file.

\(^{d}\)Estimated based on the lowest observed percentage among the other countries due to the small sample size (n = 13) and the absence of failures to meet 60% of energy target in the Screening Day study.

Abbreviations. EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay.
Sensitivity analysis – cost–benefit model
A deterministic sensitivity analysis was conducted to assess the robustness of the model-derived estimate of the overall cost–benefit ratio. The model was repeated with a ±20% variation in the value of one model parameter at a time while holding the remaining parameter values constant to assess the sensitivity of the cost estimates to the underlying assumptions.

Results
Economic burden of disease-related malnutrition
The estimated cost of illness is summarized by country in Table 3. The total estimated annual cost associated with the management of DRM-related complications in public hospitals in the eight Latin American countries is $10.19 billion. Calculation of costs using the minimum and maximum reported values for the increase in LOS due to DRM (64% and 105%, respectively) yielded a range of $8.44–$11.72 billion. Most of the increased cost observed in patients with DRM is attributable to increased LOS, which accounts for 91% and 98% of the increased costs in ward and ICU patients, respectively. Additionally, while malnourished ICU patients represent only 2.1% of all malnourished hospital patients, the management of DRM-related complications in ICU patients accounts for 12.3% of the overall DRM-related costs. The mean cost per patient is therefore 6.5 times higher for malnourished ICU patients compared with those in the ward ($5488.35 vs. $839.76; Figure 2).

The results of the deterministic sensitivity analysis are depicted in Figure 3. The analysis showed that the overall estimated cost of DRM is most strongly influenced by the following variables: number of ward patients, daily cost of stay in the ward, prevalence of DRM in the ward, and increase in LOS in ward patients with DRM.

Cost–benefit analysis: supplemental parenteral nutrition in intensive care unit patients with caloric deficits
Deterministic simulation analysis using country-specific values for clinical and resource utilization parameters yielded total annual costs of $1,134,267,485 and $1,144,423,869 in the SPN and EN groups, respectively, suggesting a total annual cost reduction of $10,156,383 with the use of SPN in patients who fail to reach the targeted energy intake with EN alone (Table 4). Use of SPN in the target population was associated with a cost reduction in each country. The largest estimated annual cost reductions were observed in Mexico ($4.66 million), Brazil ($3.28 million) and Chile ($1.93 million); more modest reductions were observed in countries such as Colombia and Ecuador in which both the average LOS and the daily cost of stay in the ICU were relatively low compared to countries with the largest estimated reductions (country-specific results are available in Supplemental File 2).

Discussion
The present study represents the first comprehensive multinational evaluation of the economic impact of DRM in Latin America. Analysis of prevalence and cost data from eight Latin American countries showed that DRM imposes a substantial clinical and economic burden, with a total estimated cost of $10.19 billion. The model-derived estimate of the cost–benefit ratio associated with SPN was most sensitive to the extent of the caloric deficit and the corresponding magnitude of effect on clinical outcomes; however, any tested variation in the values for these and other parameters led to annual cost reductions with SPN which ranged between $5.7 million and $14.4 million.

Table 3. Estimated annual economic burden of disease-related malnutrition.

| Country  |Argentina | Brazil | Chile | Colombia | Ecuador | Mexico | Panama | Peru | Total |
|----------|----------|--------|-------|----------|---------|--------|--------|------|-------|
| Ward     |          |        |       |          |         |        |        |      |       |
| Patients with DRM, \(n\) | 599,064 | 5,098,051 | 242,685 | 1,042,220 | 219,715 | 3,158,154 | 39,604 | 244,046 | 10,643,518 |
| Cost of increased LOS | 489,941,687 | 3,442,201,333 | 403,411,344 | 419,569,774 | 115,656,604 | 3,261,474,154 | 34,583,574 | 131,605,419 | 8,298,443,889 |
| Cost of HAI therapy | 49,643,914 | 323,328,732 | 3,807,135 | 9,044,809 | 12,997,124 | 235,463,753 | 1,807,240 | 3481,913 | 639,574,619 |
| Total    | 539,585,600 | 3,765,530,065 | 4,072,188,479 | 428,614,883 | 128,653,728 | 3,496,937,907 | 36,390,814 | 131,605,419 | 10,643,518 |
| ICU     |          |        |       |          |         |        |        |      |       |
| Patients with DRM, \(n\) | 19,091 | 111,892 | 11,466 | 6940 | 16,926 | 50,053 | 1677 | 10,364 | 228,408 |
| Cost of increased LOS | 36,722,443 | 640,142,277 | 644,328,655 | 14,716,641 | 31,220,717 | 415,475,578 | 6,651,156 | 27,369,461 | 1,236,626,928 |
| Cost of HAI therapy | 3,786,214 | 5,276,659 | 396,555 | 171,530 | 22,500,337 | 3,959,188 | 167,157 | 928,596 | 16,936,237 |
| Total    | 40,508,657 | 645,418,936 | 647,252,210 | 14,888,172 | 33,471,054 | 419,443,363 | 6,818,313 | 28,298,057 | 1,253,833,108 |

Total cost | $580,094,257 | $4,410,949,001 | $471,943,689 | $443,502,754 | $162,124,782 | $3,916,381,270 | $43,209,127 | $163,385,388 | $10,191,601,615 |

\(^a\)Calculated as the total estimated number of ward patients per year multiplied by the country-specific published prevalence of DRM. \(^b\)Calculated as the total estimated number of ICU patients per year multiplied by the estimated prevalence of DRM. 
Abbreviations. HAI, healthcare-associated infection; ICU, intensive care unit; LOS, length of stay.
Figure 3. Tornado diagram depicting the results of the deterministic sensitivity analysis of the economic burden associated with disease-related malnutrition. The x-axis represents the variation in the estimated cost of DRM; the y-axis lists the model parameters in decreasing order of their effect on the overall estimated cost of DRM. Abbreviations. DRM, disease-related malnutrition; ICU, intensive care unit; LOS, length of stay.
annual cost exceeding $10.19 billion. According to 2015 WHO estimates, the total health expenditure for the eight countries included in the analysis was $314 billion; our findings indicate that the incremental direct medical costs associated with DRM represent more than 3% of the total health expenditure in these countries. Notably, malnourished ICU patients account for a disproportionate share of the costs, with a 6.5-fold higher average cost per patient compared with those in the ward. This finding highlights an urgent need for the development and implementation of cost-effective strategies aimed at the early identification and effective management of patients with DRM.

A cost–benefit analysis based on clinical data from prior studies and country-specific cost data showed that administration of SPN to critically ill adults with persistent caloric deficits on EN alone a meaningful cost benefit which is principally mediated through an improvement in cumulative caloric balance and a corresponding reduction in the risk of HAI. Model-derived estimates for clinical outcomes and resource utilization suggest that the administration of SPN to ICU patients who fail to reach ≥60% of the targeted nutrition delivery with EN would yield an estimated annual cost reduction of $10.2 million across the eight Latin American countries compared with continued administration of EN alone. On average, the use of SPN resulted in net savings of $194.50 per supplemented patient, with the cost of SPN more than offset by the reduced cost of antimicrobial therapy and the shorter duration of stay in the ICU and ward. The latter benefit is particularly important, as limited bed capacity, increased demand and an increasing trend toward the use of diagnosis-related group (DRG)-based reimbursement in Latin America create a powerful incentive for public hospitals to minimize the duration of hospitalization. Coupled with the relatively low rate of SPN use observed in the Latin America Screening Day study, the cost–benefit analysis suggests that both improved clinical outcomes and significant cost savings can be achieved through the adoption of SPN as a therapeutic strategy in critically ill patients who fail to receive adequate nutrient intake from EN.

The strengths of the present study include the use of country-specific cost and population data and the conservative approach to estimating the costs associated with DRM. For example, the model only considered the incremental direct medical costs attributable to DRM rather than the full cost of hospitalization. Despite these strengths, the findings should be interpreted in the context of certain limitations. First, due to the limited availability of data for private hospitals in Latin America, the cost-of-illness calculation was based exclusively on data from public hospitals. Additionally, national values for model variables were derived from a variety of sources; in cases where information could not be retrieved from the published literature or official data sources, values were extrapolated using data from countries with publicly available information. The extent to which the

| Table 4. Clinical outcomes and medical costs based on the deterministic simulation analysis. |
|------------------------------------------------------------------------------------------|
| **Model Parameter** | **EN** | **EN + SPN** | **Difference** |
| Clinical Outcomes | | | |
| New HAI, n | 11,706 | 9711 | −1995 |
| ICU days | 837,002 | 821,600 | −15,402 |
| Ward days | 1,116,002 | 1,092,261 | −23,741 |
| Medical Costs | | | |
| Nutrition therapy | $7,539,567 | $20,691,661 | $13,152,094 |
| Antibiotic therapy | $8,317,140 | $6,898,380 | −$1,418,760 |
| ICU stay | $838,699,171 | $823,034,544 | −$15,664,627 |
| Ward stay | $289,867,991 | $283,642,901 | −$6,225,090 |
| Total cost | $1,144,423,869 | $1,134,267,485 | −$10,156,383 |

Abbreviations. EN, enteral nutrition; HAI, healthcare-associated infection; ICU, intensive care unit; SPN, supplemental parenteral nutrition.

Figure 4. Tornado diagram depicting the estimated cost benefit of SPN for all eight countries. The x-axis represents the total estimated cost–benefit ratio associated with SPN and the y-axis lists the model parameters in decreasing order of their effect on the total estimated cost–benefit ratio. Abbreviations. EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay; SPN, supplemental parenteral nutrition.
extrapolated values reflect the actual values in these countries is unknown. Moreover, the cost calculation was limited to the average daily cost of stay and antibiotic therapy; it did not account for costs associated with other common complications of DRM such as prolonged duration of mechanical ventilation or more frequent readmission. Consistent with other studies,\textsuperscript{6,10} the analyses were based on the assumption that patients with and without DRM are comparable in terms of severity of illness. Based on these considerations, our findings likely represent a conservative estimate of both the economic burden associated with DRM and the magnitude of the cost–benefit ratio associated with SPN. Finally, the magnitude of the reduction in HAI in the cost–benefit analysis was based on modeled data that showed more modest reductions in infection risk compared with estimates based on observed data, suggesting that not all of the effect of SPN is mediated through an improvement in nutrition balance.\textsuperscript{23,24} Nonetheless, the model-derived estimate was selected for the cost–benefit analysis because it represented a more conservative estimate of the clinical benefit associated with SPN.

Broad differences in study design and analytic methodologies preclude meaningful comparison of the findings with prior studies conducted in other countries. The estimated DRM-related cost per inhabitant of $20.87 is generally lower than estimates from other countries, including China,\textsuperscript{4} Croatia,\textsuperscript{7} Germany,\textsuperscript{28} the Netherlands,\textsuperscript{6} the United Kingdom,\textsuperscript{5} and the United States.\textsuperscript{1,2} The cost per inhabitant in these studies ranged from $23 in Croatia to $509 in the United States; however, the latter included both direct medical costs and quality-adjusted life years lost. A subsequent study in the United States evaluating only the direct medical costs reported an estimated cost per inhabitant of $497. The lower estimated cost per inhabitant in the present study is likely due in part to the limited number of direct medical costs included in the model, the conservative approach to estimating the effect of DRM on resource utilization and the exclusive reliance on public hospital data.

To our knowledge, only one prior study evaluated the cost–benefit ratio of SPN in ICU patients with nutrition deficits despite EN therapy.\textsuperscript{24} As noted above, the effect of SPN on clinical outcomes and resource utilization in that study was derived using the same source data as the present study; accordingly, any difference in the observed magnitude of the estimated cost–benefit ratio associated with SPN is largely attributable to regional differences in direct medical costs.

While three prior studies evaluating PN in critically ill patients had a more diverse representation of hospitals than the Swiss SPN study,\textsuperscript{23–25} none of these studies evaluated the specific indication of interest; namely, the supplemental use of PN in patients who fail to achieve nutrition targets on EN alone. The EPaNIC study\textsuperscript{23} randomized critically ill patients to receive either early PN (glucose from day 0; PN from day 2) or late PN (day 8) without regard to the presence of a firm indication for PN. The CALORIES trial\textsuperscript{21} compared 5 days of nutrition therapy with either PN or EN in critically ill patients in the UK. Consistent with the EPaNIC study, the CALORIES trial enrolled patients without regard to the presence of a clear indication for PN. The Early PN Trial,\textsuperscript{75} by contrast, compared early PN with pragmatic standard care in critically ill patients with a short-term relative contraindication to EN. More than a third of patients randomized to the control arm in the Early PN Trial received PN during the observation period, thereby potentially confounding interpretation of the findings. Therefore, among the various large randomized studies evaluating PN in critically ill patients hospitalized in the ICU, the Swiss SPN study provided the most precise estimate of the magnitude of the effect of the intervention on the outcomes of interest.

In conclusion, comprehensive analysis of prevalence and cost data from eight Latin American countries demonstrates that DRM imposes a substantial economic burden on hospitals in Latin America, with a total estimated annual cost of more than $10.19 billion. Additionally, the costs associated with DRM are more than six-fold higher in ICU patients compared with patients hospitalized in the ward. A cost–benefit analysis based on clinical outcomes from prior studies and country-specific cost data showed that optimized nutrition therapy with SPN in critically ill patients who fail to achieve ≥60% nutrition targets with EN alone improves clinical outcomes and reduces costs compared with continued administration of EN alone. These findings suggest an opportunity to implement evidence-based measures to optimize nutrition status and clinical outcomes among hospitalized patients in Latin America, thus potentially reducing the economic burden of DRM.

Transparency

Declaration of funding

This study was funded by Fresenius Kabi Deutschland GmbH.

Author contributions

All authors co-designed the study, actively discussed the study results and finalized the manuscript.

Declaration of financial/other relationships

M.I.T.D.C. has disclosed that she has served as an advisor for Abbott and Baxter and received honoraria for lectures from Abbott, Baxter, Danone, Fresenius Kabi and Nestlé. M.J.P. has disclosed that he has served as an advisor and received honoraria for lectures from Fresenius Kabi. L.P. has disclosed that he has received research grants from Fresenius Kabi for the work under consideration, and received research grants and consulting fees from Fresenius Kabi, Amgen, GSK, Roche, Jannsen Cilag, Novartis and Livanova, among others, outside of the submitted work. A.O. has disclosed that he is an employee of AdRes SRL, which has received research grants from Fresenius Kabi for the work under consideration, and received research grants and consulting fees from Fresenius Kabi, Amgen, GSK, Roche, Jannsen Cilag, Novartis and Livanova, among others, outside of the submitted work. D.L.W. has served as an advisor for Danone and received honoraria for their review work, but have no relevant financial or other relationships to disclose.

Peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no relevant financial or other relationships to disclose.
Acknowledgements
We wish to thank Kenneth Glasscock (KFG Scientific Communications, United States) for medical writing and editorial assistance.

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