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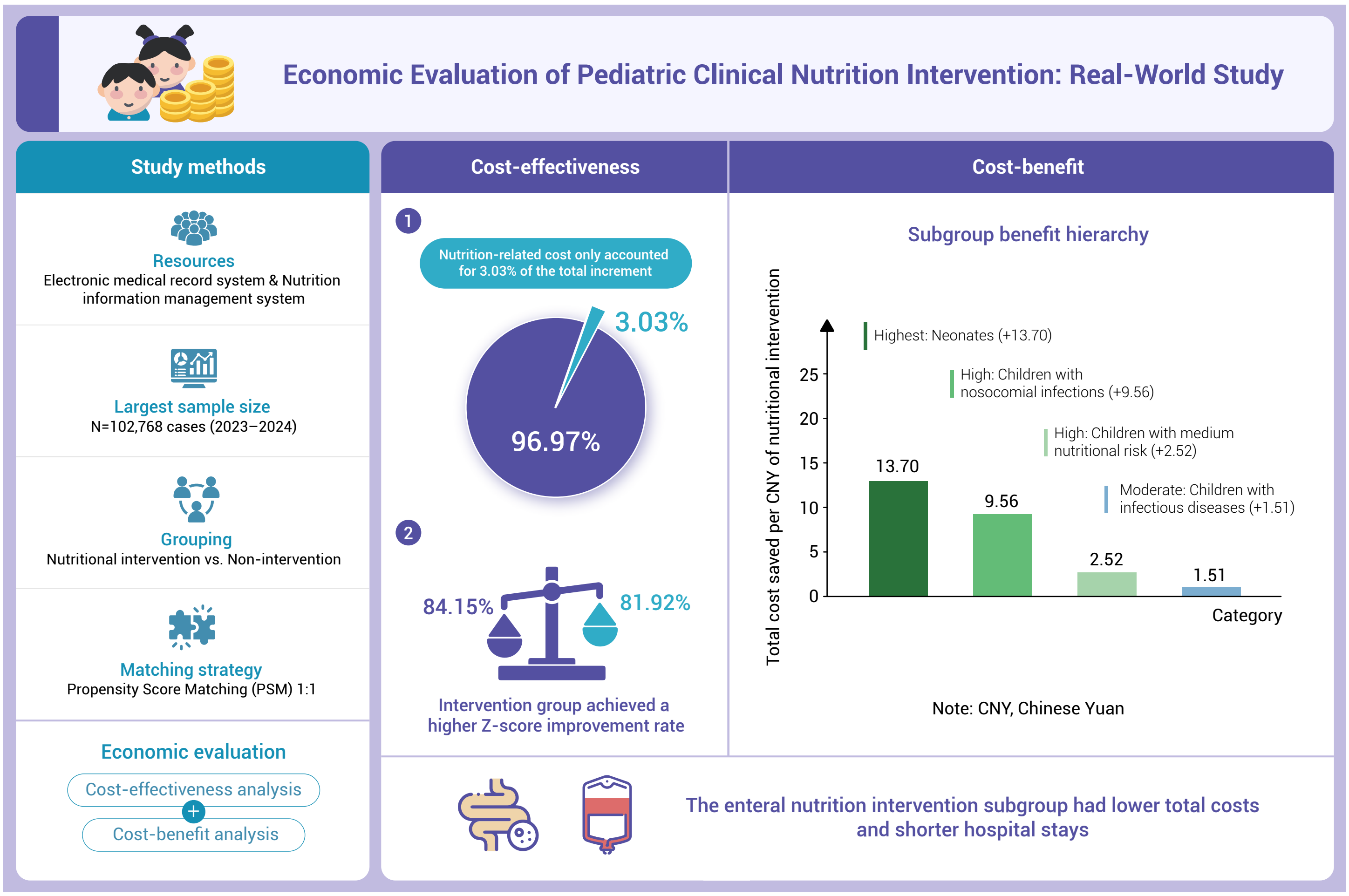
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Each Chinese Yuan (CNY) in nutritional support saves up to 13.70 CNY in total medical costs.
- Neonates and patients with nosocomial infections are the core nutritional intervention beneficiaries.
- The enteral nutrition intervention subgroup had lower total costs and shorter hospital stays.
- This study provides evidence for individualized nutrition planning and medical resource optimization.

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Pediatric inpatients are at high risk of malnutrition, which impairs their disease recovery and increases the healthcare burden, while current research remains limited in integrating treatment standardization with cost-effectiveness. We aimed to evaluate the economics benefits of pediatric nutritional interventions during hospitalization, to provide evidence for the optimal allocation of clinical nutrition resources. A retrospective observational study design was conducted, enrolling over 100,000 hospitalized children from the national pediatric medical center during 2023-2024. Participants were divided into a nutritional intervention group and a non-nutritional intervention group. Data were collected from electronic medical records and clinical nutrition information system. Primary analysis methods included propensity score matching (PSM), cost-effectiveness analysis, cost-benefit analysis. Baseline characteristics were well-balanced after matching, with all standardized mean difference (SMD) < 0.1. Nutritional interventions yielded significant benefits in specific populations such as neonates and children with nosocomial infections, where a 1-CNY investment in nutrition could save 9.56-13.70 CNY in total costs. Enteral nutrition outperformed parenteral nutrition in most subgroups. Although the total cost in the nutritional intervention group increased more, nutrition-related costs accounted for only 3.03% of the total incremental medical cost. Significant differences were revealed between the nutritional intervention group and the non-nutritional intervention group in terms of medical costs and health outcomes. There was significant subgroup heterogeneity in cost-saving, particularly among neonates and children with nosocomial infections. This study clarified the health economics positioning of pediatric nutritional interventions, providing evidence for clinical precision nutrition and optimal medical resource allocation.

INTRODUCTION

Pediatric clinical nutrition is a critical component in ensuring children's healthy growth, disease recovery, and long-term quality of life. Nutritional status not only directly affects children's growth and development but also closely correlates with the clinical outcomes of various diseases, including overall survival, treatment tolerance, infection risk, and health-related quality of life.[1] In recent years, the global attention to pediatric clinical nutrition has been growing.[2-3] In China, the National Health Commission and relevant professional societies also have attached great importance to the standardized development of pediatric nutrition services. Guidelines for the Construction and Management of the Department of Clinical Nutrition (Trial Implementation) issued in 2022 clearly stipulates that pediatric specialized hospitals at or above the second level shall establish clinical nutrition departments and provide standardized nutritional diagnosis and treatment services. A number of studies and consensus documents have pointed out that although the importance of pediatric clinical nutrition has been widely recognized, numerous challenges persist in clinical practice. Particularly, there are obvious deficiencies in standardized screening, diagnosis, treatment, and professional education, with prominent problems including non-standard nutritional screening and assessment, insufficient individualization of intervention plans, and difficulty in balancing the effectiveness and cost-effectiveness of diagnosis and treatment.

At the same time, with the continuous rise in medical costs, economic evaluations of diverse medical interventions including nutrition support-have become a global trend.[4] Multiple systematic reviews have indicated that malnutrition interventions for children under 5 years old are generally cost-effective or cost-saving in low- and middle-income countries.[5-6] However, these economic evaluation studies themselves have limitations such as the limited study age range, high methodological heterogeneity and uneven quality. Especially, there is a lack of unified standards in evaluation perspectives, cost calculation, and selection of outcome indicators, which limits the reliability and generalizability of the evidence.[6] Therefore, how to promote the standardization of pediatric clinical nutrition services at the policy level and conduct scientific economic evaluations to provide evidence-based support is an important issue that urgently needs to be addressed. Nevertheless, real-world evidence in this field remains scarce in China. To address this gap, we establish a conceptual framework illustrating the causal pathway from nutritional intervention to economic outcomes: nutritional interventions→ improvements in nutritional status (anthropometric Z-scores) and clinical outcomes (length of hospital stay, nutritional laboratory indicators) → changes in medical resource utilization (total and subvariety medical costs) → final economic outcomes evaluations.

Therefore, this study aims to systematically evaluate the health economic benefits of different nutritional intervention methods such as enteral nutrition (EN) and parenteral nutrition (PN) and intervention benefits among children with specific disease characteristics, using retrospective data of hospitalized children from 2023 to 2024 in a national children's medical center. We hypothesized that pediatric clinical nutritional interventions can improve nutrition-related and broader clinical outcomes in hospitalized children, and do such interventions generate positive economic benefits for high-risk subgroups but limited or negative economic benefits for low-risk subgroups. This study seeks to support the development of standardized pediatric clinical nutrition pathways and provide evidence for optimizing the allocation of pediatric nutrition services and balancing clinical effectiveness and cost-effectiveness in healthcare practice.

MATERIALS AND METHODS

Study design and ethics approval

This study was based on a research project entitled Establishment of Pediatric Clinical Nutrition Diagnosis and Treatment Standards and Health Economics Evaluation, and it has obtained ethical approval from the Institutional Review Board of Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine (Approval No.SCMCIRB-K2025176-1). Given the retrospective nature, no additional risk or harm to participants, and fully anonymized data processing, the requirement for written informed consent from patients or their legal guardians was formally waived by the Ethics Committee.

This study adopted a retrospective observational design integrated with health economics evaluation, with the core comparative framework of Nutritional intervention Group vs. Non-nutritional intervention Group. The intervention group included pediatric patients who received any form of nutritional support during hospitalization, such as special therapeutic diets, enteral nutrition, and/or parenteral nutrition, with existing nutrition intervention cost, excluding expense for non-clinically prescribed nutritional supplements. These interventions were formulated and implemented by the clinical nutrition team of the National Children's Medical Center based on the individualized nutritional needs of hospitalized children, and were regarded as formal nutritional interventions and an integral part of standard inpatient pediatric nutritional care. The non-nutritional intervention group comprised pediatric patients admitted during the same period who did not receive any nutritional support after hospital nutrition screening. The study population was restricted to children aged 0–18 years hospitalized between 1st January 2023 and 31st December 2024. Cases with hospitalization < 24 hours, incomplete data, or missing primary outcome indicators were excluded.

Data sources

The study data were retrieved from the Electronic Medical Record System and the Pediatric Nutrition Information Management System of Shanghai Children's Medical Center, encompassing relevant for hospitalized children from 2023 to 2024. The core datasets for analysis included: face sheet medical record data, diagnosis-related groups (DRG) data, nutrition screening and diagnosis/treatment data, clinical assessment data, laboratory test data, and other auxiliary data.

Specifically:

Face sheet medical record data contained key variables such as basic patient information, primary diagnosis, clinical outcomes and various direct hospitalization costs (e.g. drug/surgical/nursing/material cost);

DRG classification and case-mix index (CMI) values;

Nutrition-related cost data, charged via the physician order entry system, covered parenteral nutrition expenses, enteral nutrition formula costs (including additional nutritional supplements used during enteral feeding via the physician order entry system), and dietary nutrition fees;

Nutrition assessment data comprised scores from the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) and the calculation of children anthropometric Z-scores for weight-for-age (WAZs), length/height-for-age (LHAZs), weight-for-length/height (WLZs), or head circumference-for-age (HCAZs) with the World Health Organization (WHO) assertion;

Laboratory test data of nutritional status mainly included serum hemoglobin and albumin levels;

Other auxiliary data involved hospital-acquired infection status and pooling funds of basic medical insurance.

Data processing

Dataset Integration: Using hospitalization numbers and medical record numbers as key identifiers, six types of data sources (face sheet medical records, DRG classification, nutrition costs, infection records, laboratory tests, and nutrition assessments) were linked and merged to construct a unified analytical dataset.

Data Standardization: Age was standardized to years and categorized into six groups: neonates (< 1 month), infants (1–11 months), toddlers (1–2 years), preschoolers (3–5 years), school-age children (6–11 years), and adolescents (12–18 years). Gender information was standardized into three categories: male, female, and unknown. Based on the prefixes of the code of the International Statistical Classification of Diseases and Related Health Problems 11th Revision (ICD-11) for primary diagnoses, diseases were classified into nine major categories, including congenital heart disease, hematological and oncological diseases, and respiratory diseases.

Outlier Handling: The Winsorizing method was used to censor the top and bottom 1% of extreme values. Clinical rationality criteria were applied to set screening ranges for key variables: age (0–25 years), hospitalization duration (1–365 days), total medical costs (0–1,000,000 CNY), hemoglobin (30–200 g/L), and albumin (10–60 g/L). Complete list, operational definitions, and selection rationale of key variables could be found in Supplementary Table S1.

Cases with missing key variables were excluded from analysis to ensure the robustness of primary effect estimates. For example, given that CMI is a key indicator of disease severity and data imputation may introduce bias, we adopted a case deletion approach for incomplete CMI data to ensure transparency in the data processing procedure. For auxiliary variables, multiple imputation was used, which can account for the uncertainty of missing data, improve statistical power, and reduce potential bias under the missing-at-random (MAR) assumption.

Variable Definition: Patients were divided into the intervention group and non-nutritional intervention group based on whether the total cost of nutritional intervention was greater than zero. Nutritional risk was stratified into four levels using STAMP scores: low risk (0–1 points), moderate risk (2–3 points), high risk (4–6 points), and very high risk (7–9 points). Patients without STAMP scores were separately classified into the 'no STAMP score' group. Disease severity was categorized into four tiers according to CMI values: low risk (CMI < 1.0), moderate risk (1.0 ≤ CMI < 2.0), high risk (2.0 ≤ CMI < 3.0), and very high risk (CMI ≥ 3.0). Core economic indicators were constructed, including total nutritional costs, other medical costs, and nutrition-related expenses, laying a foundation for subsequent analysis.

Data Privacy Protection: Personal identifiable information was removed during data collection and processing to safeguard participants' privacy. Access to participant data was restricted, and only authorized personnel were permitted to view the datasets.

Statistical analysis

All statistical analyses were performed using R software (Version 4.4.1). All statistical tests were two-tailed, with a significance threshold set at $P< 0.05$. Descriptive statistics were used to present the baseline distribution of demographic and clinical characteristics. Between-group differences in all health outcomes were assessed as follows: independent samples t-test was used for normally distributed continuous variables, the Mann-Whitney U nonparametric test for non-normally distributed continuous variables, and Chi-square test or Fisher's exact test for small samples for categorical variables. In-depth data mining was conducted through univariate analysis, multivariate analysis, and mixed-effects models. Spearman's correlation analysis was used to examine the association between nutritional risk scores and hospitalization costs. The Kruskal-Wallis test was performed to compare cost differences across different nutritional risk groups.

Propensity score matching (PSM) was adopted to minimize selection bias and balance baseline characteristics between the nutritional intervention and non-nutritional intervention groups. A 1:1 nearest-neighbor matching without replacement was used, with CMI severity as the exact matching variable. Before PSM, we conducted grouping and categorization of the continuous CMI index according to the clinical severity classification standard. The categorical CMI variable (mild/moderate/severe) was then used as the exact matching variable in the PSM analysis. The matching variables included age, gender, CMI severity category, length of hospital stay, hospital-acquired infection (yes/no), disease category and nutritional risk stratification. A caliper width of 0.1 was set. Standardized mean difference (SMD) was applied to assess matching balance, with a threshold of SMD < 0.1 defined as the criterion for balanced baseline characteristics. Baseline characteristics were compared before and after PSM.

From the perspective of the healthcare system, the evaluation mainly adopted two methods: cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA). About CEA, the total medical costs were used as the cost indicator, while hospitalization duration and improvement rate of anthropometric Z-scores were selected as effectiveness indicators. The CBA analysis focused on quantifying the cost-saving effect of nutritional intervention.

Key evaluation indicators included incremental cost, incremental effectiveness, and incremental cost-effectiveness ratio (ICER). These indicators were used to accurately evaluate the economic efficiency of nutritional intervention.

The calculation formulas are as follows:

Incremental cost = Cost of intervention group − Cost of control group

ICER = Incremental cost / Incremental effectiveness

Subgroup analyses were conducted in this study are pre-specified in the study protocol prior to data analysis. The pre-defined subgroup factors included nutritional intervention strategies, nosocomial infection status, disease classification, and the risk level of nutritional screening. The total medical cost saved per CNY invested in nutritional intervention refers to the total inpatient medical cost saved for each CNY invested in standardized nutritional intervention in the subgroup (a negative value indicates that the intervention increases medical costs). Calculation was performed using the formula: difference in the average total medical costs between the matched non-intervention and intervention groups divided by the total direct investment in nutritional intervention for the subgroup. The economic benefit evaluation grades were classified based on the aforementioned indicator values: ≥ 2.0 CNY as highly effective, 0-2.0 CNY as moderately effective, and ≤0 CNY as negative benefit. For subgroup difference analysis, the Bootstrap method was used to perform 1000 repeated sampling simulations for estimating the 95% confidence intervals (CIs); the corresponding statistics were marked as NA if the subgroup sample size was less than 2, the observed values were completely missing, or the simulation results showed no stable distribution. CI crossing zero is not equivalent to the traditional P-value-based judgment of statistical significance, as the 95% CI herein is used primarily to reflect the reliability and degree of variation of cost-benefit estimates rather than test statistical significance.

For the two highly confounding factors of length of hospital stay and nutritional intervention costs, this study conducted further sensitivity analysis: a new PSM rule was adopted to correct the confounding effect of length of hospital stay, with matching variables including age, gender, CMI severity, disease categories, nutritional screening risk grouping, surgical status (surgical/non-surgical) and medical payment methods, and a Love plot and Propensity Score (PS) distribution curves were used to visualize the matching effect. After that, stratified analysis was performed for nutritional intervention costs, where the study population (excluding outliers beyond±2SD) was divided into four groups based on the mean and standard deviation (SD) of total nutritional costs in the intervention group (low-cost: -2SD~-1SD, low-medium cost: -1SD~mean, medium-high cost: mean~+1SD, high-cost: +1SD~+2SD), followed by subgroup economic benefit analysis to verify result stability.

Quality assurance

Comprehensive quality control was implemented throughout data collection and processing, including data completeness checks, logical consistency verification, and final dataset construction. This involved evaluating the matching rate of merged datasets from different sources, analyzing the missing rate of key variables, and identifying and resolving duplicate records. In addition, logical consistency verification was conducted mainly to examine the logical relationship between hospitalization duration and medical costs, verified the rationality of the changing trend of laboratory indicators, and confirmed the chronological order between nutritional intervention and clinical outcomes.

Due to the retrospective nature of data collection and the non-randomized study design, this study is prone to various types of bias. To address selection bias, PSM was used for rigorous adjustment. For information bias, a unified health economics data extraction form was developed to clarify the extraction criteria for cost data and effectiveness data, and data authenticity verification was performed. Regarding confounding bias, stratified analysis and sensitivity analysis were conducted according to key confounding factors, and the cost-effectiveness of nutritional intervention was calculated separately across different strata to verify the consistency of intervention effects in different populations. Cases with missing key variables were excluded and auxiliary variables were handled using multiple imputation under the MAR assumption to reduce potential bias. Meanwhile, baseline equivalence comparison was performed in this study to further control the interference of intergroup differences on the results.

RESULTS

Baseline characteristics

A total of 102,768 hospitalized pediatric patients (69,656 in the intervention group and 33,112 in the non-nutritional intervention group) were initially enrolled from 2023 to 2024. After data cleaning, standardization, and multiple imputation of missing values, an analytical dataset containing key variables such as demographics, clinical diagnosis and treatment, and cost data was established. Proportion of missing values in core variables and corresponding handling strategies can be seen in Table S2 for details. Table S3 presents the baseline equivalence comparison of demographic and clinical characteristics among matched samples.

As shown in Table 1 and Figures 1–4, regarding the demographic characteristics, male patients accounted for 59.8%, with school-age children (39.6%) being the dominant group, followed by preschoolers (22.1%). In terms of clinical characteristics, 51.7% of the patients were classified as low-risk based on CMI, 98.2% had no hospital-acquired infections, and respiratory diseases were the most common condition (10.9%). For the collected core variables, total medical cost was right-skewed (mean: ¥23,513; median: ¥10,434). The average length of hospital stay was 5.60 days, and the median nutrition-related cost was ¥30, and most patients incurred no nutrition-related cost. Nutritional risk was predominantly categorized as low (42.2%) and moderate (41.3%). The anthropometric Z-scores mostly ranged from -2 to 2. There was no significant change in albumin levels before and after hospitalization (paired analysis results: +0.29 g/L, 95%CI: -0.008-0.60, P=0.06), while hemoglobin levels exhibited a statistically significant upward trend (+13.05 g/L, 95%CI: 10.87-15.22), P < 0.01). The Kruskal-Wallis test verified that the differences in total hospitalization costs among different nutritional risk groups were highly statistically significant (P < 0.001).

Validation of Propensity Score Matching (PSM) results

We performed 1:1 nearest neighbor matching strategy for the PSM procedure, with CMI severity as the exact matching variable. Matching covariates included Matching covariates included CMI values, length of hospital stay, standardized age, infection status, and disease category, with a caliper width set at 0.1. Patients were successfully matched from the initial sample of 102,768 cases (the matching success rate was approximately 61%), with 31,302 cases in each group.

Balance tests indicated that prior to matching, the standardized mean differences (SMD) of variables including age, gender, length of hospital stay, CMI severity, disease category, and nutritional risk classification were imbalanced to varying degrees, with some variables showing SMD exceeding 0.1. After matching, the SMD of all variables dropped significantly to below 0.045, far lower than the balance criterion of 0.1, indicating a substantial improvement in the balance of baseline characteristics. Comparison of core characteristics between the two groups post-matching revealed no statistically significant differences in key indicators, including age, gender distribution, CMI severity, length of hospital stay, and hospital-acquired infection rate. After propensity score matching, the nutritional intervention group and the non-nutritional intervention group achieved high comparability in terms of demographic characteristics, disease severity, resource consumption, and clinical features (Table 2).

Health economics evaluation results

The overall cost-effectiveness analysis demonstrated significant differences in medical costs and health outcomes between the two matched groups (Table 3). In terms of costs, the average total cost of the nutritional intervention group was ¥16,912, which was ¥5,078 higher than that of the non-nutritional intervention group (¥11,834), representing a relative increase of 42.9%. Cost composition analysis showed that the cost increase in the intervention group was mainly attributed to other medical expenses (¥16,758 vs ¥11,834), while nutrition-related costs accounted for an extremely low proportion. Specifically, the average PN cost was ¥60.77, and the average EN cost was ¥92.96, totaling ¥153.73, which only accounted for 3.03% of the total cost increase. This indicates that the cost increase was not directly attributable to nutritional intervention itself, but rather by the fact that patients requiring nutritional intervention were often associated with greater consumption of other medical resources.

Regarding health outcomes, the average length of hospital stay in the intervention group (4.05 days) was statistically significantly longer than that in the non-nutritional intervention group (3.50 days). Among the effectiveness indicators, the improvement rate of anthropometric Z-scores in the intervention group (84.15%) was slightly higher than that in the non-nutritional intervention group (81.92%), indicating that nutritional intervention had a certain effect on improving nutritional status.

Incremental cost-effectiveness analysis further quantified the economic efficiency of pediatric nutritional intervention. The results showed that the incremental cost of ¥5,078.15 incurred by the intervention group compared with the non-nutritional intervention group yielded differential benefits corresponding to different effectiveness indicators. In terms of length of hospital

Table 1. Basic data characteristics (n=102,768).

Category	Specific indicators	Classification/Statistic	Frequency (n)/ Mean ± SD	Percentage (%)/ Median
Demographic characteristics	Gender	Male	61,415	59.8
		Female	41,353	40.2
	Age group	Neonates (< 1 month)	3,741	3.6
		Infants (1-11 months)	8,643	8.4
		Toddlers (1-2 years)	9,200	9.0
		Preschool age (3-5 years)	22,672	22.1
		School age (6-11 years)	40,647	39.6
		Adolescents (12-18 years)	17,574	17.1
Clinical characteristics	CMI severity	Low risk (CMI< 1.0)	53,119	51.7
		Medium risk (1.0≤CMI<2.0)	4,848	4.7
		High risk (2.0≤ CMI< 3.0)	2,875	2.8
		Very high risk (CMI≥ 3.0)	7,901	7.7
	Hospital-acquired infection status	No nosocomial infection	100,915	98.2
		With nosocomial infection	1,853	1.8
Medical expenses & Hospitalization	Total cost (CNY)	-	23,513 ± 43,872	10,434
	Length of hospital stay (days)	-	5.60 ± 8.7	3
	Nutrition cost (CNY)	-	115 ± 349	30
Nutritional risk	Nutritional risk stratification	Low risk (0-1 points)	43,373	42.2
		Medium risk (2-3 points)	42,423	41.3
		High risk (4-6 points)	6,596	6.4
		Very high risk (7-9 points)	398	0.4
Disease category	Disease type	Other diseases	47,043	45.8
		Respiratory diseases	11,159	10.9
		Nervous system diseases	9,612	9.4
		Urinary system diseases	8,029	7.8
		Congenital heart disease	7,982	7.8
		Digestive system diseases	4,957	4.8
		Injuries and poisoning	4,764	4.6
		Perinatal diseases	3,911	3.8
		Infectious diseases	2,782	2.7
		Hematological and oncological diseases	2,481	2.4

Notes: '-' indicates no corresponding statistic.

stay, the intervention group had a 0.55-day longer stay than the non-nutritional intervention group, with an incremental cost-effectiveness ratio (ICER) of -¥9,298.96 per reduced hospital day, indicating that the nutritional intervention represents a dominated strategy, as it is less effective and more costly than the comparator, and therefore has no economic advantage. The improvement rate of anthropometric Z-scores was the sole positive incremental indicator: the intervention group had a 2.24% higher rate than the non-nutritional intervention group, with an ICER of ¥2,269.82 per 1% increase in improvement rate, and its cost-effectiveness needs to be further judged in combination with the clinical willingness-to-pay threshold. Given the absence of established willingness-to-pay (WTP) thresholds for improvements in anthropometric Z-scores among pediatric nutritional interventions in both domestic and international literature, no fixed WTP benchmark was applied in this economic evaluation.

Subgroup analysis further revealed significant heterogeneity in the health economics evaluation across different types (Tables 4 & 5). In the neonatal subgroup (< 1 month), PN intervention demonstrated prominent cost-saving effects: every ¥1 invested reduced total costs by ¥13.70, thus being rated as a 'high-efficiency' intervention. For patients with nosocomial infections, EN combined with dietary intervention showed better effectiveness, with every ¥1 invested reducing total costs by ¥9.56, also falling into the 'high-efficiency' subgroup. For patients with infectious diseases, both PN and EN interventions showed 'moderate efficiency', with every ¥1 invested reducing total costs by ¥1.14 and ¥1.51, respectively. On the contrary, for subgroups including patients without nosocomial infection, those with low nutritional risk, those with hematological and oncological diseases, and those with congenital diseases, the cost savings per CNY invested in the intervention for each subgroup were all negative (ranging from -56.77 to -5.28), and the

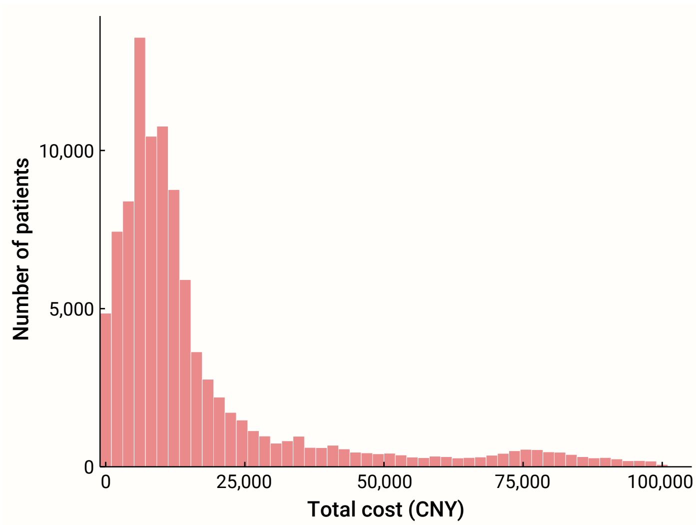

Figure 1. Total medical expenses for hospitalized pediatric patients.

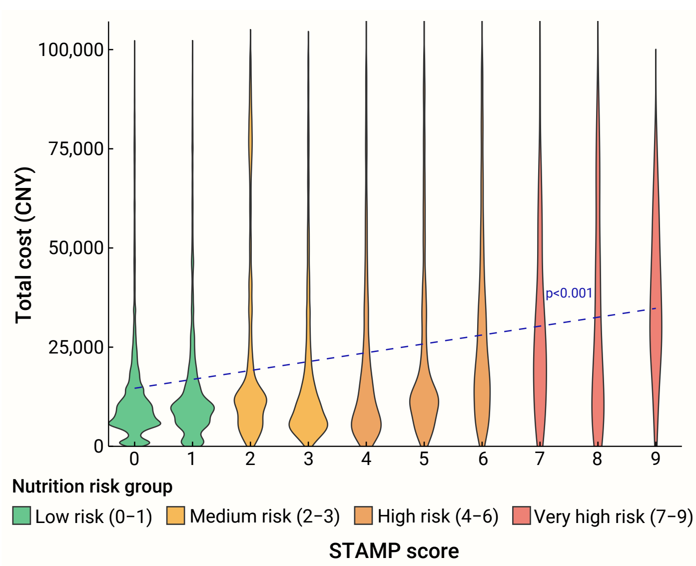

Figure 2. Relationship between nutritional risk screening scores and total hospitalization costs (Violin Plot-Correlation Composite Plot)

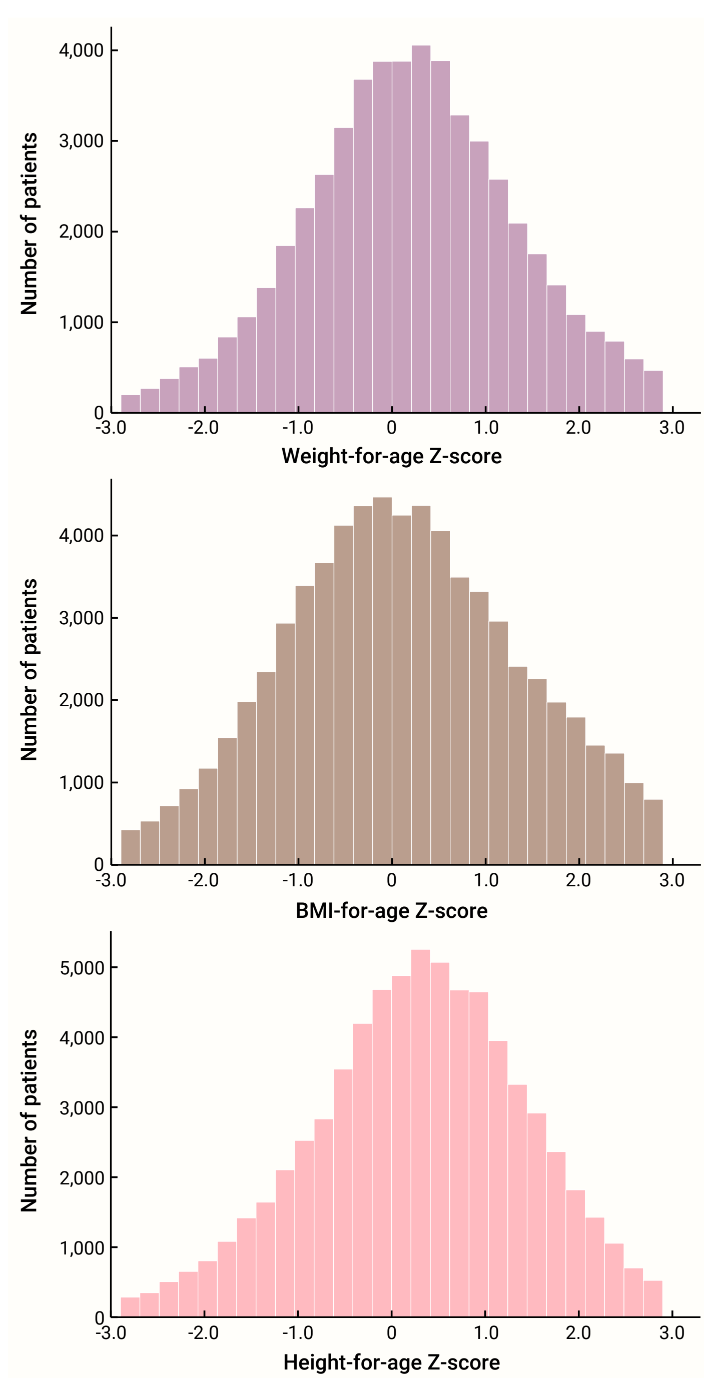

Figure 3. Distribution of Z-scores for anthropometric growth status of hospitalized pediatric patients. Note: Anthropometric Z-scores (weight/height-for-age, weight-for-length/height) were calculated per WHO growth standards. Z-score near 0 denotes normal growth; negative values <-2 indicate malnutrition-related growth impairment. This distribution reflects the baseline growth heterogeneity of the study population and provides a standardized metric for evaluating nutritional intervention effects and identifying high-risk subgroups.

economic benefit evaluation results were ‘negative benefit’. These results indicate that the cost-effectiveness of nutritional intervention is closely related to the type of pediatric disease, with infection status and special physiological stages being key factors affecting the benefits.

With the increase in intervention intensity, total costs, length of hospital stay, and nutrition-related costs all increased significantly. Comparison of different nutritional intervention types showed that patients in the combined PN+EN intervention group had the most severe conditions, with an average total cost of ¥161,337, an average length of hospital stay of 41.3 days, and a Z-score improvement rate of 85.2%. The PN-only intervention group had an average total cost of ¥94,864 and an average length of hospital stay of 23.4 days. The EN-only intervention group had the widest application, with an average total cost of ¥15,548, an average length of hospital stay of 3.70 days, and a anthropometric Z-score improvement rate of 84.6%.

Sensitivity analysis

After updating the PSM algorithm, the matching rate decreased to 29%. Detailed matching results are presented in Table S4 &Figure S1 - S2. In the low-medium cost of nutrition intervention group, the most significant cost-saving effects were observed in the benefit subgroups. Children with nosocomial infections constituted the largest beneficiary population, with every 1 CNY invested in nutritional care reducing total medical expenses by 158.70 CNY. Children with infectious diseases and hematological malignancies also showed notable cost-saving effects, with each 1 yuan of nutritional expenditure reducing total medical costs by 60.68 CNY and 40.47 CNY, respectively (see Table S5).

DISCUSSION

As an important part of the National Children's Medical Center, the CMI of Shanghai Children's Medical Center is characterized by high stability and continuous growth, consistently ranking among the top national children's hospitals- this reflects its core strength in treating difficult and critical pediatric cases, laying a solid foundation for large-sample, high-quality clinical

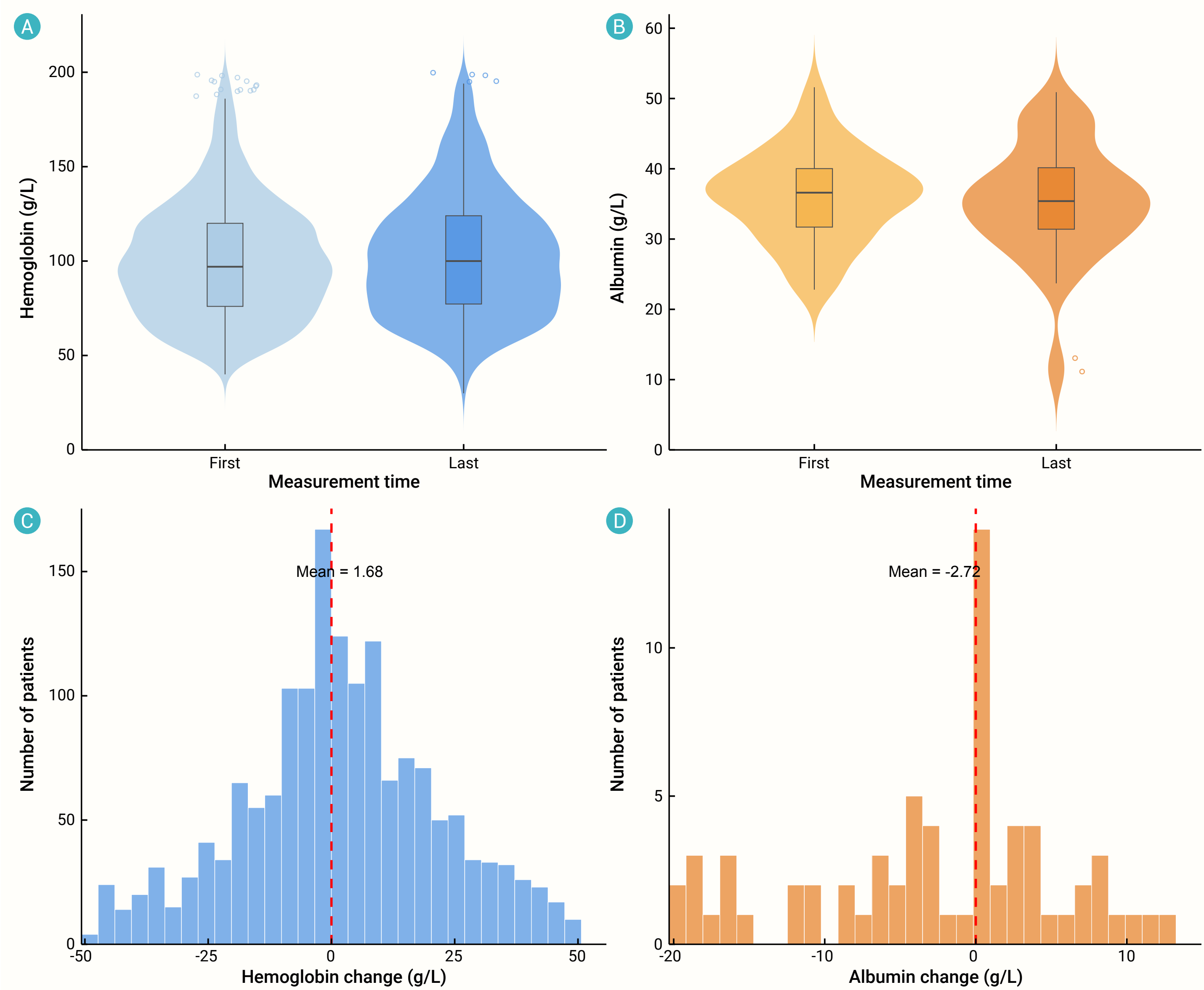

Figure 4. Comparison of serum hemoglobin and albumin levels before and after hospitalization, along with distribution of change values. A: Distribution of hemoglobin levels at first vs. last measurement B: Distribution of albumin levels at first vs. last measurement. C: Distribution of hemoglobin change (mean increase: 1.68 g/L). D: Distribution of albumin change (mean decrease: 2.72 g/L). Note: Paired t-tests showed a highly significant increase in hemoglobin levels post-intervention (+13.05 g/L, 95%CI: 10.87-15.22, P< 0.01), while albumin levels showed a non-significant modest rise (+0.29 g/L, 95%CI: -0.008-0.60, P=0.06), reflecting individual variability in albumin improvement.

research. Based on the largest-sample-size study on pediatric nutritional health economic evaluation, the analysis showed that the total cost of the nutritional intervention group was ¥5,078 higher than that of the non-nutritional intervention group, while the increase in nutrition-related costs accounted for only 3.03% of the total cost increment, with a slightly higher Z-score improvement rate (84.15% vs 81.92%). Significant subgroup heterogeneity was observed: neonates, patients with hospital-acquired infections, and those with moderate nutritional risk were identified as high-efficiency beneficiary populations of nutritional intervention, whereas populations without infections and with low nutritional risk exhibited negative benefits. Different intervention types yielded similar improvement effects, but enteral intervention and therapeutic diets had the lowest cost and the widest application. As the first domestic study supported by over 100,000 all-age pediatric samples from a national medical center, this research, combined with the high CMI advantage, helps establish an integrated framework linking standardized pediatric nutrition care with economic efficiency.

International evidence indicates that pediatric nutritional interventions are generally cost-effectiveness.[7] A systematic review published in 2022 aimed to assess the quality of economic evaluations of child nutrition interventions in low- and middle-income countries (LMICs) and synthesize research characteristics and economic evidence. By searching 9 electronic databases, the study identified all interventions related to malnutrition, including stunting, wasting, micronutrient deficiencies, and overweight, and included 69 economic studies on child nutrition interventions conducted in LMICs (mainly from sub-Saharan Africa and South Asia). Mortality rate, intervention effect, intervention coverage, cost, and discount rate were reported as predictors for sensitivity analysis. Despite the potential heterogeneity and publication bias among the included studies, 81% of the studies concluded that nutritional interventions were cost-effective or cost-beneficial, primarily based on the cost-effectiveness thresholds of respective countries.[5] It is worth to note that, anthropometric Z-score is as a continuous indicator reflecting nutritional status improvement in this study, and no unified national or industry-wide WTP standard is currently available. Therefore, the cost-effectiveness of nutritional interventions was assessed using a comparative approach focused on the cost-effectiveness relationship, specifically the incremental medical cost associated with a 1% increase in the Z-score improvement rate, to support clinical decision-making and healthcare resource allocation rather than determining absolute cost-effectiveness against a predefined WTP cutoff.

Although generally cost-effective, the economic efficiency of different

Table 2. Validation of PSM results.

Variable	SMD before matching	SMD after matching	Balance improvement	Nutritional intervention group(n=31,301)	Non-nutritional intervention group (n=31,301)	P value
Age (years)	0.027	0.005	Good	6.72 ± 4.29	6.75 ± 5.01	0.124
Gender (Male proportion)	0.021	0.012	Good	18,545 (59.2%)	18,492 (59.1%)	0.856
Length of Hospital Stay (days)	0.432	0.038	Significant improvement	6.72 ± 9.81	6.68 ± 9.75	0.342
Hospital-acquired Infection Rate	0.105	0.022	Good	698 (2.2%)	705 (2.3%)	0.782
CMI Severity	0.411	0.015	Significant improvement	1.04 ± 1.37	1.02 ± 1.35	0.215
Disease Category	0.537	0.042	Significant improvement	-	-	-
Nutritional Risk Stratification	0.641	0.028	Significant improvement	-	-	-

Notes: Matching strategy: 1:1 nearest neighbor matching; Exact matching variable: CMI severity; Matching variables include CMI severity, length of hospital stay, age, infection status, and disease category; Caliper value=0.1; '-' indicates no directly comparable inter-group values, and balance is only evaluated by SMD.

Table 3. Overall and incremental cost-effectiveness results of pediatric nutritional intervention.

Evaluation dimension	Specific group/Type	Sample size	Total cost	PN cost	EN cost	Other medical costs	Length of hospital stay (days)	Physical Z-score improvement rate (%)	Incremental cost	ICER
Overall cost-effectiveness	Non-nutritional intervention group	31,302	11,834	0	0	11,834	3.5	81.92	-	-
Overall cost-effectiveness	Nutritional intervention group	31,302	16,912	60.77	92.96	16,758	4.05	84.15	5,078.15	-
Incremental cost-effectiveness	Length of hospital stay	-	-	-	-	-	-	-	5,078.15	-9,298.96 (CNY / 1 day reduction)
Incremental cost-effectiveness	Physical Z-score improvement rate	-	-	-	-	-	-	-	5,078.15	2,269.82 (CNY / 1% increase)

Notes: '-' indicates no corresponding data or no need to fill in; Incremental Cost = Total Cost of Intervention Group - Total Cost of Control Group; ICER calculation logic: Incremental Cost ÷ Incremental Effect. The incremental effect of length of hospital stay is negative (intervention group is longer than control group), so ICER is negative. Negative values indicate increased costs, while positive values indicate cost savings.
Abbreviations: ICER: Incremental Cost-effectiveness; PN: Parenteral Nutrition; EN: Enteral Nutrition.

interventions is influenced by multiple factors, including intervention type, implementation setting, age of the target population, and economic-related inequality.[8-10] Previous studies, with relatively consistent conclusions, have mainly focused on childhood obesity interventions and digital health interventions.[11-14] A 2023 review incorporating 31 systematic reviews pointed out that interventions combining nutrition and physical activity showed effectiveness and cost-effectiveness across all age groups, especially in community settings.[15] Another systematic review published in 2023, which comprehensively analyzed 151 studies, similarly found that most interventions targeting childhood overweight and obesity were considered cost-effective compared with usual care.[16] A secondary data analysis based on randomized controlled trials (RCTs) evaluated a school-based obesity intervention program, and the results showed that the comprehensive intervention combining nutrition education and physical activity was cost-effective and cost-saving, with a cost-utility ratio (CUR) of ¥11,505.9 per quality-adjusted life year (QALY) and a cost-benefit ratio (CBR) of ¥1.2 benefit per ¥1 invested.[14] Another systematic review published in 2023 analyzed 22 economic evaluations of digital health interventions (DHIs) for children and adolescents, and found that 82% of the studies indicated that DHIs were cost-effective or cost-saving compared with traditional non-digital interventions.[6]

In terms of nutritional therapy for specific pediatric diseases, economic evaluations also demonstrate their application value, with Crohn's disease (CD) as a typical example. A cost-effectiveness analysis published in 2025 used a Markov model to evaluate the effect of specialized formulas versus standard oral nutritional supplements (ONS) in the treatment of children with mild-to-moderate CD under the UK National Health Service. The results showed that compared with standard ONS, the use of specialized formulas could save £591 per patient per year while maintaining similar QALYs, with a 78% probability of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY.[17] However, even for the same disease, healthcare systems and payment models in different countries or regions may affect the optimal cost-effective strategy.[18] For example, amino acid formulas (AAF) and extensively hydrolyzed formulas (eHF) for formula-fed infants show national and regional differences in pharmacoeconomic studies related to the diagnosis, management, and prevention of cow's milk protein allergy.

Prominent cost-saving benefits observed in neonates and patients with nosocomial infections, while hematologic malignancy patients exhibited negative economic returns in our subgroup analysis, suggesting that disease type, infection status and physiological stage substantially influence the economic value of nutritional support. Neonates have immature digestive and metabolic functions and limited nutritional reserves, placing them at high nutritional risk. And in children with nosocomial infections, inflammatory

Table 4. Subgroup cost-benefit analysis of significant results.

Evaluation dimension	Specific group/type	Sample size (n)	Total cost saved per CNY of nutritional intervention (CNY) (95% CI) *	Economic benefit evaluation
PN intervention	Neonates (< 1 month)	1,134	13.70 (-180.95, 255.35)	Highly effective
PN intervention	Medium nutritional risk (2-3 points)	23,599	2.52 (-14.19, 22.44)	Highly effective
PN intervention	With nosocomial infection - Other diseases	215	2.35 (-15.54, 26.04)	Highly effective
PN intervention	Infectious disease patients	1,562	1.14 (-15.41, 32.09)	Moderately effective
EN intervention	With nosocomial infection - Other diseases	215	9.56 (-63.84, 87.86)	Highly effective
EN intervention	Neonates (< 1 month)	1,134	2.99 (-19.90, 20.71)	Moderately effective
EN intervention	Infectious disease patients	1,562	1.51 (-25.70, 29.53)	Moderately effective
EN intervention	Medium nutritional risk (2-3 points) patients	23,599	1.12 (-6.89, 8.91)	Moderately effective
Subgroup analysis (negative benefit)	Patients without nosocomial infection	61,847	-36.48 (-39.39, -33.59)	Negative benefit
Subgroup analysis (negative benefit)	Low nutritional risk patients	44,278	-56.77 (-61.11, -52.42)	Negative benefit
Subgroup analysis (negative benefit)	Hematological and oncological disease patients	971	-13.74 (-23.99, -9.77)	Negative benefit
Subgroup analysis (negative benefit)	Perinatal disease patients	1,203	-5.28 (-13.56, -3.96)	Negative benefit

Notes: * indicates that 95% CIs are primarily used to reflect the reliability and degree of variation of cost-benefit estimates, and thus whether an indicator's CI crosses zero does not correspond to the traditional P-value-based judgment of statistical significance. Abbreviations: PN: Parenteral Nutrition; EN: Enteral Nutrition.

Table 5. Subgroup cost-effectiveness analysis of intervention types.

Specific type	Sample size	Total cost (CNY)	PN cost (CNY)	EN cost (CNY)	Other medical costs (CNY)	Length of hospital stay (days)	Physical Z-score improvement rate (%)
PN + EN	245	161,337	6,430	883	154,024	41.3	85.2
PN only	88	94,864	3,715	0	91,149	23.4	83.7
EN only	30,969	15,548	0	87.0	15,461	3.70	84.6

Abbreviations: PN: Parenteral Nutrition; EN: Enteral Nutrition.

catabolism and malnutrition jointly delay recovery. Nutritional intervention may enhance immune function, thereby facilitating infection control, potentially shortening hospital stay, and reducing associated medical costs. It is also reasonable that pediatric patients with hematologic malignancies typically present with complex conditions, where the therapeutic focus lies in survival rates and disease control rather than cost-effectiveness. Consequently, the cost-effectiveness profile is suboptimal, necessitating hierarchical management of clinical resource allocation based on tumor type, disease stage, and treatment objectives, rather than adopting a one-fits-all universal solution. However, the sensitivity analysis revealed a relatively positive trend, which was particularly pronounced in the subgroup with low-to-moderate nutritional intervention costs, which essentially reflects the divergent economic outcomes of non-stratified generalized intervention versus risk-targeted precise low-cost nutritional support for this population. Similarly, the WHO systematic review (2021) confirmed that supplementary feeding efficacy is modified by disease severity and nutritional status, justifying our disease classification subgroup. This validates the rationale for including intervention methods and disease category as prespecified subgroups in our study. However, it should be noted that all subgroup analyses in this study are primarily intended for hypothesis generation and clinical reference, rather than providing definitive conclusions. Given the inherent limitations of subgroup comparisons, the observed findings need to be further validated and confirmed by well-designed prospective studies with larger sample sizes.

At the same time, we highlight a profound question: in real-world clinical settings that need to cover different age groups, disease types, and treatment options, whether pediatric nutritional interventions still maintain stable clinical effectiveness (e.g., improvement of nutritional status, optimization of health outcomes) and health economics value (e.g., cost control, efficient use of resources); whether there is clear stratification of beneficiary populations; and whether the applicable scenarios of different intervention modes (enteral, parenteral, and combined interventions) are clear, which still need further research verification and clarification. In recent years, domestic scholars have carried out health economics evaluations of nutritional support mainly in multiple adult fields such as oncology, severe burning, and PN+EN combined nutritional support, achieving a series of results, while relevant evidence for pediatric nutrition remains limited.[19-20] Compared with our previously published data of us results from the same national children's medical center during 2017–2018,[21] we found that hospitalized children during 2023–2024 had higher nutritional risk screening scores, which were associated with higher average total hospitalization costs, drug costs, and antibiotic costs. This indicates that in recent years, the nutritional risk of hospitalized children in this center is closely related to the severity of their illness and the intensity of treatment interventions: higher nutritional risk screening scores are often associated with more complex underlying diseases, higher infection-related risks, or heavier disease burdens, which in turn lead to increased demand for medical interventions such as drug use and antibiotic anti-infection treatment during hospitalization, ultimately pushing up the average total hospitalization costs and related sub-item costs. It is urgent to strengthen the early identification of nutritional risk and targeted intervention in clinical practice to reduce the risk of complications and optimize the efficiency of medical resource utilization. In addition, the longer length of hospital stay observed in our nutritional intervention group should not be interpreted as an adverse effect attributable to the intervention itself. Instead, it primarily reflects the higher baseline disease severity and greater clinical complexity among patients who received nutritional support. In clinical practice, pediatric inpatients with more severe conditions, complex comorbidities, or poor nutritional status are more likely to be referred for nutritional interventions by clinicians, and the natural progression of their underlying diseases inherently results in prolonged hospital stays. Regarding the generalizability, it should be noted that although this study has the largest sample size in the field of pediatric nutritional health economic evaluation in China, the results limited the extending of conclusions to primary care facilities or community health service centers with limited pediatric resources, as well as to geographically or socioeconomically diverse pediatric populations.

This study is the first pediatric nutritional intervention research in China supported by a full-age-range cohort of over 100,000 pediatric participants, with outstanding representativeness and extrapolability. It precisely identified the core beneficiary groups via multi-dimensional subgroup analyses, and constructed a rigorous analytical framework by integrating PSM for bias control, multiple statistical methods, as well as cost-effectiveness and cost-benefit analyses, thereby providing scientific evidence for clinical precision nutritional interventions and optimal allocation of pediatric medical resources. However, the study has certain limitations. First, the retrospective data are susceptible to the impact of unmeasured confounding factors such as care conditions, standardization of intervention duration and dosage consistency. Second, the lack of long-term follow-up data makes it impossible to evaluate the long-term benefits of nutritional interventions. In addition, from a macro healthcare system and health insurance payment perspective, this health economics evaluation only focused on direct medical costs from the perspective of medical institutions, excluding indirect costs (such as labor costs and parental lost work time). Meanwhile, the uneven geographical and disease-specific distribution of samples, together with insufficient refined data, may lead to biases in the conclusions. Furthermore, health economics evaluations of nutritional interventions, especially in pediatrics, faces broader challenges, including low quality of evidence, ambiguous long-term effects, incomplete assessment of health outcomes, insufficient evidence for specific populations and emerging intervention models, incomplete cost accounting, and lack of equity analysis.[22] These common issues limit the reliability and comparability of conclusions in this field.

In view of the limitations of the present study, including regional and resource bias, potential confounding from its retrospective design, and the short-term study perspective, we propose the following directions for future research: Conduct well-designed randomized controlled trials with concurrent economic evaluations to improve the quality of evidence; establish long-term follow-up cohorts to collect data on the sustainability of nutritional intervention effects and long-term health economic outcomes; develop and validate multi-dimensional outcome indicators covering cognitive function, family well-being and quality of life,[23] and exploring monetization methods for non-health outcomes; conduct targeted research on evidence gaps to strengthen cost-benefit analyses for specific populations and novel interventions; adopt a societal perspective for comprehensive cost accounting to accurately assess the overall social value of interventions; integrate equity analysis into routine research processes and providing evidence for health equity decision-making through subgroup analyses; and promote the formulation of specialized methodological guidelines and reporting standards to enhance the transparency, comparability and overall quality of research. From top-level design to practical implementation, synergistic efforts are required to advance the construction of standardized methodologies, precision intervention practices, long-term follow-up monitoring, comprehensive cost-benefit accounting, equity considerations and social value translation. These strategies will systematically address current challenges in the health economic evaluation of pediatric nutritional interventions and lay a solid foundation for evidence-based clinical and policy decision-making.

CONCLUSION

For the first time based on large-sample real-world data from the National Children's Medical Center/ Shanghai Children's Medical Centre in China, this study clarifies the clinical effectiveness, health economics value, and population and scenario adaptability of pediatric nutritional interventions during hospitalization, filled the evidence gap for refined research, and provides scientific decision-making support for the clinical precise implementation of nutritional interventions and the optimal allocation of medical resources.

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The author responsibilities were as follows: D. Su contributed to data analysis and original manuscript drafting; Z. Weng, J. Yuan, Y. Wang and B. Zhang: project promotion and data collection; L. Pan, S. Guo and H. Li corresponding authors: project conception, supervision and manuscript revision. All authors agreed to the final manuscript's submission to this journal.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Due to concerns pertaining to medical security, the original data generated and analyzed during the current study are not publicly available. For any research-related inquiries, please contact the corresponding author.