



Exploring the Generalizability of Foreign Cost-Effectiveness Analysis to Spain Using Data From a Scoping Review of Multinational Studies

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Abstract

Objective This study examines the generalizability of foreign economic evaluations to the Spanish healthcare system. The research aims to describe the cross-country adaptation methods identified in a scoping review of multinational cost-utility analyses and to examine the probability of concordant funding decisions between Spanish and foreign results, as well as to identify factors influencing generalizability.

Methods First, a scoping review of multinational studies reporting cost-utility analyses for at least two countries, including Spain, was conducted using MEDLINE, PubMed, Embase and Web of Science in April 2025. Data related to transferability were extracted and a narrative synthesis was performed. Second, a dataset of case comparisons—each defined as a technology against a comparator in a specific population—was developed from the identified studies. Each foreign comparison was matched to its Spanish equivalent within the same study. Incremental cost-effectiveness ratios (ICERs) were converted to 2024 Spanish Euros and compared against a threshold of €30,000 per quality-adjusted life year (QALY). A multilevel logit model was used, with a binary variable indicating decision concordance between Spanish and foreign ICERs/dominance as the dependent variable. We also analysed the distances in the incremental costs and incremental QALYs between countries using a log-normal bivariate model. Country-specific and other study-related factors were considered as independent variables in both models.

Results The review included 57 studies. Most were funded by drug manufacturers and conducted in Europe. The majority of authors did not specify their reasons for selecting countries. All but three studies attempted to use local costs, probabilities and/or epidemiological data. Twelve studies incorporated country-specific utilities. A total of 644 comparisons were analysed; 142 were Spanish results and 502 were foreign results with their Spanish equivalents. The cost-effectiveness plane quadrant of the foreign result matched the Spanish result in 84% of cases. Assuming a threshold of €30,000 per QALY, the funding decisions were the same in 93% of cases. The probability of decision concordance was higher when the study was conducted in a Eurozone country or in the United Kingdom. Sensitivity analysis showed the variability of decisions depending on the selected cost-effectiveness threshold. Similar variables were found as relevant factors explaining the distance in the incremental QALYs analysis.

Conclusion Foreign cost-effectiveness results of those studies analysing drugs from Eurozone countries such as France, Germany, Italy, or from the United Kingdom can often be generalizable and provide meaningful insights for decision making in Spain. However, these findings should not be used as a reason to avoid country-specific studies if they are feasible. Further research is needed to determine if these findings apply to other health technologies. Limitations of the study include the lack of a formal assessment of the methodological quality of the selected studies and the potential risks of bias.

1 Introduction

In Spain, as in other countries, the decisions on public reimbursement of health technologies are guided by criteria such as safety, effectiveness and cost effectiveness [1–3].

A cost-effectiveness analysis is a full economic evaluation where costs and effects of at least two alternatives are compared [4]. If a technology is less costly and more effective than the comparator then it is considered dominant. However, it is more frequent to find cases where the technology is more effective but also costlier than the comparator [5]. In such cases, the incremental cost-effectiveness ratio (ICER)

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Key Points for Decision Makers

Most multinational cost-utility analyses do not justify their selection of countries, rarely discuss transferability and almost all used local costs.

In most of the cases analysed, the Spanish and foreign results showed agreement in terms of cost effectiveness and funding decisions for any of the thresholds used.

In general, evidence on the cost effectiveness of a drug from the Eurozone or the United Kingdom could be generalisable and used to inform decision making in Spain.

is calculated, denoting the ratio of the difference in costs to the difference in effects between the alternatives. When the effects are expressed in quality-adjusted life years (QALYs), the ICER could be compared against an incremental cost-effectiveness threshold to inform decisions about reimbursing the new technology within the public healthcare system [6]. Although Spain has not explicitly stated the use of a threshold, the cost effectiveness is one of the criteria considered to make decisions according to the law and some authors have proposed threshold estimates for Spain [7, 8].

Whenever a health authority wants to make decisions based on cost-effectiveness criteria, the evidence could come from economic evaluations submitted by companies and/or conducted by health technology assessment (HTA) agencies, universities or hospitals. In Spain, the first option is not always available as it is not mandatory for the companies to present cost-effectiveness analyses and they often report budget impact analyses rather than economic evaluations [9]. The second option is time-consuming and expensive, and given the number of new health technologies, it is necessary to prioritise the technologies to be assessed by public bodies [10–12]. When an economic evaluation cannot be conducted because of time restrictions and/or budgetary constraints, the HTA could be replaced by a systematic review of economic evaluations. However, using systematic reviews to reach conclusions on cost effectiveness is controversial [13]. Specifically, the results of economic evaluations are not directly generalizable across countries because of the differences in costs, health care provision systems and reimbursement schemes, for example [12, 14]. Unlike transferability, which focuses on adapting foreign studies to local conditions, generalizability evaluates whether conclusions from one setting can be directly used in local contexts without substantial modifications [12]. If we consider transferability as a continuum, then the maximum transferability is equivalent to generalizability of results [15].

To assess the generalizability is not an easy task. In this study, we focus on a practical and limited definition of generalizability: the concordance in hypothetical funding decisions across countries based on the comparison between the ICER and a given cost-effectiveness threshold.

Barbieri et al. analysed economic evaluations of medicines conducted in two or more Western European countries published from 1988 to 2001 to study the causes of variation in results across countries and elicit if those variations were systematic and important for decision making [16]. They included 46 comparisons of drugs taken from 67 studies (29 comparisons in multi-country studies and 17 comparisons in single-country studies) and concluded that the cost-effectiveness results varied across countries in Western Europe. The type of study (trial-based study or model) had some impact, but the most important factors were effectiveness, resource use and unit costs. The variations were not systematic so direct generalization between countries would not be straightforward [16]. Barbieri et al. [16] also found that the multi-country studies were the best source of evidence on variation in cost-effectiveness results between countries as the same methodology was used across all countries. Boehler and Lord [17], some years later, used multilevel statistical modelling to integrate cost-effectiveness estimates from published economic evaluations of statins to investigate causes of within- and between-country variations. They aimed to explore whether between-country variation could be explained by national characteristics, such as GDP. Unexpectedly, they found a relatively low proportion of variation attributable to the country level (14–19% of total variance), with differences in study methods accounting for the majority of the variability of cost-effectiveness estimates [17].

There are guidelines on how to conduct systematic reviews of economic evaluations [18–20] and tools to assess their generalizability and transferability [21, 22]. Spanish guidelines for conducting economic evaluations [23–28], consistent with internationally accepted methods [4, 29], have recommended over the years that data sources should be as close as possible to the local context where they are going to be used. Moreover, these guidelines state that transparency in methods and results facilitates the assessment of the transferability of the economic evaluation [23–28]. Nevertheless, the focus of this article is not on the transferability of studies, but on the generalizability of cost-effectiveness results. These guidelines establish that generalizability requires adherence to national guidelines and this demands quality assessment of the studies. Our approach, however, focuses on a narrower definition, analysing whether foreign results and Spanish results would lead to the same reimbursement decision.

Building on the work of Barbieri et al. [16], this study explores the generalizability of foreign economic evaluations to the Spanish healthcare system using a two-step approach:

first, a scoping review of multinational economic evaluations including Spain, and second, a subsequent statistical analysis. This is broken down into three sub-objectives: to describe whether and how the analyses were adapted to country-specific contexts within each study; to analyse the probability of reaching the same decision about funding or not funding the health technology based on both the Spanish and the foreign results; and to explore the factors influencing generalizability by means of Bayesian statistical analyses. Considering the growing interest in transferability across countries [22, 30], and given that the issue of generalizability remains an open question, we propose this study to address a gap in the literature. Specifically, it examines the concordance and proximity of decisions based on foreign versus local cost-effectiveness data from the Spanish point of view, offering helpful insights in contexts where time or resource constraints impede the generation of local cost-effectiveness evidence.

2 Methods

First, we carried out a scoping review of multinational economic evaluations to achieve the first research objective (see Sect. 2.1). The review is presented according to the PRISMA-ScR standards for scoping reviews [31]. Second, we performed a statistical analysis to address the second and third objectives (see Sect. 2.2).

2.1 Scoping Review

2.1.1 Eligibility Criteria

We selected full model-based economic evaluations and full economic evaluations conducted alongside primary experimental or observational studies. The selected studies had to report outcomes in QALYs. The population consisted of humans with a health condition where any intervention or health technology could be assessed. The comparator could be any alternative, including a ‘control group’ or ‘no intervention’. Following Barbieri’s approach and given the objective of the study, we selected multinational studies where the same scope (population, intervention and comparator) was analysed for at least two countries, with Spain as one of the countries. Studies were also required to report the ICERs or dominance. We excluded partial economic evaluations, letters, editorials and conference proceedings.

2.1.2 Information Sources and Search

The search was conducted in PubMed, MEDLINE, Embase and Web of Science (WOS), in April 2025. It included

three groups of terms combined with the Boolean connector AND: economic evaluation, Spain and names of other countries based on World Bank list [32]. Language limits were not used. The full search strategy is available in Supplementary file 1 (Tables S1–S3), see electronic supplementary material (ESM).

2.1.3 Selection of Sources of Evidence, Data Charting Process

One researcher (economist) screened titles and abstracts, followed by full-text reviews of eligible articles, and extracted the relevant data. A second researcher (economist) verified the selection and data extraction. Data extracted from the selected studies included details about the population (disease according to ICD-10), the technology and comparator, methods used in the analysis (i.e. type of model, time horizon, discount rates, perspective, included costs, currency, threshold, sensitivity analysis), funding sources and results (incremental costs, incremental QALYs, ICERs or dominance). Incremental results and dominance were extracted from the sensitivity analysis only if they were the result of comparing relevant modifications of the alternatives, results of subgroup analysis or a different perspective from the base case. That is, results from sensitivity analysis related to modification of time horizon, discount rates and values of parameters (such as effectiveness, costs, use, adherence and other probabilities) were not extracted. Other specific and relevant details related to transferability were collected: countries included and reasons for selecting those countries; whether the model was *de novo* or adapted from a previous one; the software used for modelling; whether the sources of data for Spain were Spanish (for effectiveness, use of resources, costs or other parameters); whether part of the sample was Spanish in primary studies; whether differences in results between countries were discussed; and methods used to adapt data across countries.

2.1.4 Synthesis of Results of the Scoping Review

Given the purpose of this scoping review, we did not assess the methodological quality of the included studies. Rather, we performed a narrative synthesis (supported by tables) and separately described the characteristics of the studies more directly related to the transferability of findings across countries. The foreign ICERs and incremental costs were converted to 2024 Spanish Euros using purchasing power parity (PPP) to adjust for differences across countries and gross domestic product (GDP) deflator index to adjust for time-period differences [33]. Following Barbieri et al. [16], when the results were reported in Euros for non-Euro

countries (United Kingdom, for example) and conversion rates were reported, ICERs were reconverted to the national currency before adjusting for PPP and GDP deflator index. If conversion rates were not reported, ICERs were not adjusted using PPP (as if they were already ‘Spanish’ Euros), and only adjusted by the GDP deflator index.

2.2 Statistical Analysis

For the second and third subobjectives, we built a dataset of cases defined as comparisons of a technology against a comparator in a specific population extracted from the multinational studies. Each comparison extracted from a foreign country (any country different from Spain) was matched to its equivalent comparison for Spain reported in the same study (irrespective of the extended dominance results in order to avoid losing comparisons). At least one case for each study was identified. The cost effectiveness (potential decision) of both the Spanish and the foreign results (ICER or dominance) was determined according to €30,000 per QALY [8, 34]. Therefore, it was possible to obtain a binary variable named ‘Same_decision’, with value = 1 when the hypothetical decisions based on cost effectiveness with both the Spanish and the foreign ICER/dominance were the same (this is what we call ‘decision concordance’), zero otherwise. This binary variable was the dependent variable in a multivariate multilevel logit model specified to identify the factors associated with the probability of making the same decision, where the levels refer to the comparisons grouped within the studies.

While assessing whether decisions in Spain align with those in other countries is the primary aim of generalizability, we additionally explore the degree of divergence between the conclusions reached in Spain and those drawn elsewhere. We opted not to use the difference in ICERs as ICERs—being ratio-based—are inherently unstable and highly sensitive to variation, particularly when the denominator approaches zero. Instead, we propose a bivariate modeling approach for incremental cost and incremental QALYs. Specifically, the endogenous variables are defined as the percentage differences between the incremental QALYs and incremental cost estimated for Spain and those estimated for other countries. For this analysis, we used multilevel log-normal models for seemingly unrelated equations. Both models (multilevel logit and multilevel log-normal models) were estimated using a Bayesian approach [35]. The technical details are provided in Supplementary file 2 (see ESM).

All independent variables tested in the regression, except one, were dichotomous variables representing attributes of interest extracted from the foreign cost-effectiveness studies (see Table S4 in Supplementary file 1, ESM). These included the most prevalent group of diseases in the sample (diseases of the circulatory system or digestive systems and

cancer), the type of technology (drug, vaccine), whether the comparator was no treatment, whether a Markov model was used, whether the time horizon was 5 years or shorter, whether only direct medical costs were included in the analysis and whether the study was funded by the developer of the technology. The countries with the largest number of cases in the sample were included as independent variables. Other country-specific variables were built, that is, a variable representing whether the foreign country was a member of the Eurozone at the time of the evaluation and a variable representing whether the country had a social security system (SSS) (see Table S5 in Supplementary file 1, ESM). The only continuous variable included in the model was the number of years since the reference year for costs, as obsolescence of interventions, data and even methods can affect the relevance of results [36].

Sensitivity analyses were conducted considering other thresholds close to €30,000 per QALY and used as alternative thresholds in Spain, that is, €25,000 and €35,000 per QALY [7, 8, 37].

Analyses were conducted using Stata, version 17.0 (Stata-Corp, College Station, Texas 77845 USA) and OpenBUGS, version 3.2.3 (MRC Biostatistics Unit, University of Cambridge, UK).

3 Results

3.1 Scoping Review

3.1.1 Characteristics of the Multinational Studies

The search yielded 2146 references without duplications. After screening against criteria selection, 57 studies [38–94] were included in the scoping review (Fig. 1). Of these, 55 were model-based economic evaluations and two were clinical trials. The studies were published between 2006 and 2025. Their main characteristics are summarized in Table 1. All but nine studies were funded by manufacturers of technologies that were evaluated in those studies. The number of countries analysed in each study ranged from two to ten. Most of them were European countries; the most frequently included countries were the United Kingdom, Italy, Germany, France and Sweden. Out of the 57 studies, 18 evaluated technologies for diseases of the circulatory system, seven for endocrine diseases, seven for neoplasms (cancer) and six for diseases of the musculoskeletal system. The other groups of diseases were less frequent in the identified studies. For 12 ICD-10 chapters, no studies were identified. In 67% of the studies, the evaluated technology was a drug. Although there was a variety of type of models, the most frequent was the Markov model (32 studies). The time horizon was long term or lifetime in most studies. In 89% of

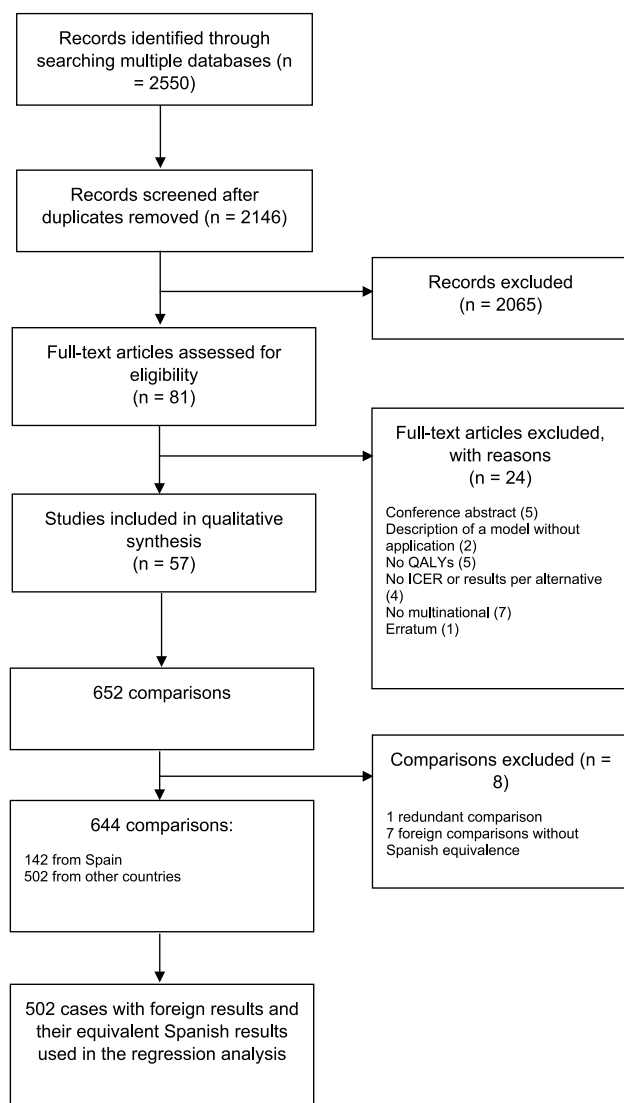


Fig. 1 Flow diagram. (ICER incremental cost-effectiveness ratio, QALYs quality-adjusted life years)

studies, the perspective was that of the health care system and only direct medical costs were included in the analysis. More details for each study can be found in Supplementary file 3 of the ESM.

In 43 studies, only two alternatives were compared, in eight studies there were three alternatives and in six studies there were four or more alternatives. Nineteen studies conducted subgroup analysis as well. None of the studies reported results for all countries using more than one perspective. Three studies contributed to the sample with only one comparison. If we analysed the distributions of comparisons among the foreign results, that is, all countries except Spain, we can observe that the maximum number of comparisons in a unique study was 56 and reported for eight countries [66]. The number of comparisons per

country varied from one to nine. The latter corresponded to a study that reported 18 comparisons for only two countries (Germany and the United Kingdom) [62].

Consequently, 57 studies produced 652 comparisons. Eight were excluded: seven foreign comparisons without Spanish equivalence and one redundant comparison (a study included separated results for England and Scotland, dominance in both cases; we used only one of them to compare Spain with the United Kingdom). Overall, out of the 644 comparisons, 142 were Spanish results whereas 502 were results for foreign countries with their equivalent Spanish results. The latter 502 were included in the statistical analysis (Fig. 1).

3.1.2 Explanation for the Transferability of Studies

Most studies (35 out of 57; 61%) did not state the reasons for selecting the countries in the corresponding economic evaluations. In seven studies, the countries were selected because they participated in the trials used as the main source of effectiveness; in six studies, the reason was just that the selected countries had a large population. Other studies reported varied reasons such as the difference in prices/costs between countries [38, 43, 72]; differences in interventions (vaccination calendar for influenza) [53]; differences in disease risk [43, 72]; or the opposite, namely, similarities in disease burden, costs, treatments and health systems [46]; or just the fact that there were not previous models for those countries [45, 53]. Only two studies explicitly acknowledged that cost-effectiveness results from one country were not transferable to other countries, hence the need for country-specific analysis [50, 54], and another two stated differences in the financial/reimbursement systems [78, 86].

Twenty-seven studies were the application or adaptation of a previous study. In four of them, the authors talked about an application [55, 64, 69, 75], but in most of the studies the authors explicitly said that they adapted a previous model. Twelve studies used Excel sheets for their models and three used R for some analysis. Seven studies used licensed and cost-effectiveness-oriented software: five studies used TreeAge, three used the CORE Diabetes Model and one used Simul8. Apart from one of the models that is available upon request [94], another one is currently freely available [65], and only one group of authors shared their model as supplementary material [89].

All but three of the studies tried as much as possible to use local costs and local probabilities (of clinical events or death, for example) and/or epidemiological data. Twelve studies used country-specific utilities also. One study varied only resource use (and exceptionally one local unit cost) [44]. Most studies (63%) reported all results in Euros for all countries, 9% reported only US dollars, while 26% reported more than one currency. Among those studies that

Table 1 Characteristics of multinational economic evaluations

Characteristic	No. of studies (% out of 57 studies)
Disease, ICD-10 Chapters ^a	
Chapter I. Certain infectious and parasitic diseases	3 (5%)
Chapter II. Neoplasms	7 (12%)
Chapter IV. Endocrine, nutritional and metabolic diseases	7 (12%)
Chapter V. Mental and behavioural disorders	2 (3%)
Chapter VI. Diseases of the nervous system	2 (3%)
Chapter IX. Diseases of the circulatory system	18 (32%)
Chapter X. Diseases of the respiratory system	4 (7%)
Chapter XI. Diseases of the digestive system	4 (7%)
Chapter XIII. Diseases of the musculoskeletal system and connective tissue	6 (10%)
Chapter XIV. Diseases of the genitourinary system	3 (5%)
Type of technology	
Drug	38 (67%)
Vaccine	2 (3%)
Device	3 (5%)
Surgery/procedure	5 (9%)
Test	4 (7%)
Other	5 (9%)
Type of comparator	
Another specific drug/device or current treatment/practice	40 (70%)
Control/no treatment/placebo	17 (30%)
Type of study	
Randomized clinical trial	2 (3%)
Markov model	32 (56%)
Decision tree model	4 (7%)
Discrete event simulation model	2 (3%)
Hybrid model	7 (12%)
Other type of model	10 (18%)
Time horizon	
≤ 1 year	5 (9%)
> 1 year & ≤ 5 years	11 (19%)
> 5 years & ≤ 10 years	6 (10%)
> 10 years and lifetime	35 (61%)
Discount used for Spain	
3%	33 (58%)
3.5%	12 (21%)
6%	5 (9%)
Not reported	3 (5%)
No discount	4 (7%)
Perspective	
Health system	51 (89%)
Societal ^b	8 (14%)
Hospital	1 (2%)
Costs included in the analysis	
Only medical costs	48 (84%)
Other ^b	9 (16%)
Currency	
Euro for all countries	36 (63%)
Pound Sterling for all countries	1 (2%)

Table 1 (continued)

Characteristic	No. of studies (% out of 57 studies)
USA Dollar for all countries	5 (9%)
More than one currency	15 (26%)
Method used for conversion of ICERs and costs from national currencies to a common currency	
No conversion conducted, each country reported in their own currency	25 (44%)
Results converted to a reference currency using exchange rates; exchange rates reported by authors	14 (25%)
Results converted to a reference currency using exchange rates; exchange rates unreported	4 (7%)
Results converted to a reference currency using PPP	3 (5%)
Unreported or unclear method	11 (19%)
Sensitivity analysis	
Both deterministic and probabilistic analysis	32 (56%)
Only deterministic analysis	19 (33%)
Only probabilistic analysis	3 (5%)
None	3 (5%)
Threshold	
Only one regardless the country:	
<€20,000 per QALY	1 (2%)
20,000-30,000 £ or € per QALY	11 (19%)
>€30,000 per QALY	2 (3%)
No explicit	15 (26%)
None	9 (16%)
Country-specific threshold:	
Depending on the GDP	2 (3%)
€30,000 per QALY for Spain, some other threshold for other countries	9 (16%)
<€30,000 per QALY for Spain, some other threshold for other countries	5 (9%)
>€30,000 per QALY for Spain, some other threshold for other countries	3 (5%)
Type of funding	
Private funds	48 (84%)
Grants from public bodies	5 (9%)
Not reported	3 (5%)
No funding	1 (2%)
Countries (other than Spain)	
United Kingdom (or England or England and Wales or Scotland)	33 (58%)
Italy	32 (56%)
Germany	29 (51%)
France	25 (44%)
Sweden	15 (26%)
Belgium	10 (18%)
The Netherlands	6 (10%)
Austria, Finland, Portugal	4 (7%)
Denmark, Greece, USA	3 (5%)
Australia, Brazil, Canada, Hungary, Ireland, Norway, Switzerland, Taiwan	2 (3%)
Czech Republic, Japan, New Zealand, Poland, Singapore	1 (2%)
Country-specific parameters	
Epidemiology	31 (54%)
Costs	54 (95%)
Resource use	11 (19%)
Effectiveness	2 (3%)
Utilities	12 (21%)
Threshold	21 (37%)

Table 1 (continued)

Characteristic	No. of studies (% out of 57 studies)
Other factors relevant for transferability	
Adapted from or application of a previous model	27 (47%)
Software under licence but broadly used	13 (23%)
Software under licence but expensive or very specific	7 (12%)
Model available	2 (3%)

Note: The sum is > 40 in several items as the categories are not always exclusive

GDP gross domestic product, *ICD* International Classification of Diseases, *ICER* incremental cost-effectiveness ratio, *PPP* purchasing power parity, *QALY* quality-adjusted life years

^aOnly ICD chapters with results are reported here, that is, for those ICD chapters not mentioned here, the number of studies was 0

^bFour studies declared the use of the societal perspective in sensitivity or secondary analysis but did not report numerical results for all countries. Another study did not report the perspective but we could consider it societal as it included direct medical costs and informal care. Three studies explicitly reported societal perspectives, including productivity losses or informal care. Only one study included only medical costs plus other direct costs.

converted ICERs from national currencies to a common currency, most of them used exchange rates which were reported in the study (25%). Only three studies used PPP values for the conversion [51]. Four studies did not report the exchange rates used and eleven studies did not explain sufficiently the method used.

3.2 Statistical Analysis

3.2.1 Comparison of Results and Decisions Between Spanish and Foreign Studies

In 421 cases (321+11+0+89) out of 502 (83.9%) the cost-effectiveness plane quadrant of the foreign result matched that of the Spanish result; most cases (321) were in the north-east quadrant, that is, where the technology is costlier and more effective than the comparator (Table 2). The foreign results and the Spanish results did not match in the

same quadrant in some cases; most non-matched cases occupied the north-east and south-east quadrants (Table 2).

As the north-east quadrant includes ICERs that make the technology cost effective or not cost effective depending on the threshold, we assumed a threshold (€30,000 per QALY) to classify the results of that quadrant and obtained cost-effectiveness-based decisions for the whole cost-effectiveness plane (Table S6 in Supplementary file 1, see ESM). Assuming such threshold, in 92.6% ((367+98)/502) of the cases the decisions were the same: below the threshold in 78.9% (367/(367+98)) of cases (cost-effective technology, including dominant technologies) and above the threshold in 21.1% (98/(367+98)) of cases (no cost-effective technology, including dominated technologies). The decisions were the same in 93.0% and 92.4% of the cases for thresholds of €25,000 and €35,000 per QALY, respectively (data not shown in tables).

Table 2 Distribution of foreign cases and Spanish cases in the quadrants of the cost-effectiveness plane

Foreign cases	Spanish cases				Total
	North-East	North-West	South-West	South-East	
	More effective and costlier	Less effective and costlier	Less effective and less costly	More effective and less costly	
North-East					
More effective and costlier	321 (63.9%)	0	1 (0.2%)	52 (10.4%)	374 (74.5%)
North-West					
Less effective and costlier	0	11 (2.2%)	1 (0.2%)	0	12 (2.4%)
South-West					
Less effective and less costly	0	0	0	0	0
South-East					
More effective and less costly	27 (5.4%)	0	0	89 (17.7%)	116 (23.1%)
Total	348 (69.3%)	11 (2.2%)	2 (0.4%)	141 (28.1%)	502 (100%)

3.2.2 Factors Influencing Generalizability

The first column of Table 3 shows the results of the multilevel logit model ($N = 502$) for a threshold of €30,000 per QALY. Five variables were found to be relevant and associated with the concordance in decisions if we consider as relevant those variables whose estimated coefficients have a probability of direction $> 95\%$. On the one hand, the probability of concordance was very high when the study was conducted in a country within the Eurozone (OR 8.01; $p = 0.9999$). This would mean that the probability of concordance in decisions between Spanish and foreign studies when the country was in the Eurozone would be eight times the probability of those cases where the country was not within the Eurozone. To the Eurozone effect we must add the specific effect in two countries: France (OR 13.03; $p = 0.9904$) and Italy (OR 19.69; $p = 0.9886$). Therefore, the probability of concordance in decisions between Spanish and French or Italian studies would be 104 and 157 times higher, respectively, than the probability of those cases where the country was not within the Eurozone. Although it does not belong to the Eurozone, the probability of concordance is also high in studies from the United Kingdom (OR 13.21, $p = 0.9999$). On the other hand, the odds of decision concordance between Spanish and foreign studies were lower when the comparator was no treatment (OR 0.007, $p = 0.9813$).

If we also consider as relevant those variables whose estimated coefficients have a probability of direction $> 90\%$, we also found that the probability of concordance was high when the study was conducted in Germany (OR 4.38, $p = 0.9222$) and when the study evaluates a drug (OR 128.12, $p = 0.9113$). However, the probability of concordance decreases when the disease was one of the digestive system (OR 0.003, $p = 0.9096$) or when the study used a Markov model (OR 0.01, $p = 0.9053$).

Some changes in the relevant variables are observed when the threshold is €25,000 per QALY (Table 3, second column). In this model, the only relevant country was the United Kingdom (OR 8.29, $p = 0.9994$) besides the Eurozone (OR 11.05, $p = 0.9996$). The odds of decision concordance between Spanish and foreign studies remained low when the comparator was no treatment (OR 0.03, $p = 0.9706$). In this analysis, the age of the study emerges as a relevant variable, with a higher probability of concordance observed when the studies were recent (OR 0.62, $p = 0.9999$). By considering variables as relevant when their probability of direction exceeds 90%, we observed that the probability of concordance was low for diseases of the circulatory system (OR 0.06, $p = 0.9351$) and high in privately funded studies (OR 107.99, $p = 0.9245$). No new relevant variables were detected in the model when the threshold was €35,000 per QALY (Table 3, third column).

In a complementary analysis, we tried to identify predictors of the discrepancies in incremental cost and incremental QALYs between Spain and other foreign countries. Table 4 shows the results of the multilevel log-normal model for incremental cost and incremental QALYs, assuming equations that are apparently unrelated ($N = 418$). The descriptive analysis of the model variables (Table S4 in Supplementary file 1, see ESM) revealed greater differences in the estimation of incremental costs between Spain and other foreign countries, in comparison with the differences in incremental QALYs. These differences were higher with the United Kingdom ($\exp(\text{coef}) = 1.47$, $p = 0.9681$) and Germany ($\exp(\text{coef}) = 1.56$, $p = 0.9827$), and were also greater in older studies ($\exp(\text{cost}) = 1.07$, $p = 0.9804$). On the other hand, the discrepancies in incremental costs were smaller when comparing with Italy, when the disease was part of the circulatory system, or when a Markov model was employed in the analysis ($\exp(\text{coef}) = 0.63$, $p = 0.9227$).

Regarding the differences in incremental QALYs, these differences were smaller for Eurozone countries ($\exp(\text{coef}) = 0.59$, $p = 0.9857$)—namely France ($\exp(\text{cost}) = 0.59$, $p = 0.9569$) and Italy ($\exp(\text{coef}) = 0.57$, $p = 0.979$)—as well as for diseases related to the digestive ($\exp(\text{coef}) = 0.03$, $p = 0.9963$) and circulatory systems ($\exp(\text{coef}) = 0.38$, $p = 0.9242$). In contrast, discrepancies are larger when the study is older ($\exp(\text{coef}) = 1.1$, $p = 0.9568$), when the technology under evaluation is a vaccine ($\exp(\text{coef}) = 20.76$, $p = 0.921$) and when the health system is SSS ($\exp(\text{coef}) = 1.43$, $p = 0.9229$).

4 Discussion

The aim of this research was to analyse the generalizability of foreign economic evaluations to the Spanish healthcare system, where generalizability is defined as the concordance in the decisions based on the comparison of ICERs and cost-effectiveness thresholds between countries.

Fifty-seven articles were included in the scoping review of multinational economic evaluations. Most authors did not disclose the reasons for conducting and publishing multinational studies, and those who did, argued differences and similarities across countries, particularly in terms of costs, interventions or health care systems. Few of them referred to the lack of transferability across countries or about having their models available, perhaps because most of them were funded by industry. The authors focused their efforts on the ‘cost’ parameter to adapt their analysis across countries.

From these 57 studies, a total of 502 cases where a scope for a foreign country coincided with one for Spain were extracted to build a database used for the statistical analysis. The distribution of the results of the comparisons in

Table 3 Odds ratios of the predictors of dependent variable 'same decision' for different thresholds

Variable	Estimate	Dependent: Same_decision (when threshold is...)		
		€30,000 per QALY	€25,000 per QALY	€35,000 per QALY
UK	OR	13.21	8.29	17.2
	95% CI	(3.03–69.69)	(2.31–35.34)	(3.49–110.83)
	Prob	0.9999	0.9994	0.9999
France	OR	13.03	2.17	2.65
	95% CI	(1.44–141.17)	(0.38–13.83)	(0.5–15.64)
	Prob	0.9904	0.7963	0.8679
Germany	OR	4.38	2.63	2.06
	95% CI	(0.61–35.73)	(0.4–21.74)	(0.4–11.16)
	Prob	0.9222	0.8313	0.7998
Italy	OR	19.69	3.29	4.93
	95% CI	(1.48–339)	(0.34–42.35)	(0.6–55.92)
	Prob	0.9886	0.8444	0.9276
Eurozone	OR	8.01	11.05	6.9
	95% CI	(2.62–28.11)	(2.71–50.55)	(2.28–23.22)
	Prob	0.9999	0.9996	0.9998
SSS	OR	1.01	0.84	0.76
	95% CI	(0.3–3.23)	(0.2–3.56)	(0.23–2.44)
	Prob	0.5204	0.553	0.6626
Circulatory_disease	OR	0.39	0.06	0.47
	95% CI	(0–254.42)	(0–2.92)	(0–134.29)
	Prob	0.6165	0.9351	0.6216
Digestive_disease	OR	0.003	0.02	0.005
	95% CI	(0–11.82)	(0–70.39)	(0–24.09)
	Prob	0.9096	0.8606	0.8992
Cancer	OR	0.01	1.04	0.02
	95% CI	(0–51.11)	(0–18,676.1)	(0–54.87)
	Prob	0.862	0.605	0.8618
Drug	OR	128.12	0.26	63.62
	95% CI	(0.15–53,637.3)	(0–48.13)	(0.21–10,270.18)
	Prob	0.9113	0.6949	0.9131
Vaccine	OR	1.58	0.77	1.62
	95% CI	(0–189,094.09)	(0–634,124.13)	(0–20,150.81)
	Prob	0.539	0.6046	0.5659
Comparator_notreatment	OR	0.007	0.03	0.007
	95% CI	(0–0.76)	(0–1.12)	(0–0.38)
	Prob	0.9813	0.9706	0.9943
Markov	OR	0.01	0.44	0.01
	95% CI	(0–4.38)	(0–39.81)	(0–2.18)
	Prob	0.9053	0.7192	0.9465
Horizon_0_5	OR	0.03	0.08	0.07
	95% CI	(0–40.61)	(0–14.45)	(0–47.99)
	Prob	0.802	0.8282	0.7585
Only_DMC	OR	2.01	1.84	1.76
	95% CI	(0.02–5710.15)	(0.07–3118.17)	(0.02–569.07)
	Prob	0.6919	0.8042	0.6567
Years_old	OR	0.74	0.62	0.78
	95% CI	(0.37–1.15)	(0.26–0.85)	(0.54–1.14)
	Prob	0.8918	0.9999	0.8927

Table 3 (continued)

Variable	Estimate	Dependent: Same_decision (when threshold is...)		
		€30,000 per QALY	€25,000 per QALY	€35,000 per QALY
Private_funds	OR	2	107.99	1.42
	95% CI	(0–1639.26)	(0.32–8,202,913.88)	(0–1144.82)
	Prob	0.5004	0.9245	0.5087
Cons	Coef.	11.25	10.68	10.52
	95% CI	(2.21–26.95)	(3.72–24.86)	(3.54–19.81)
	Prob	0.9953	>0.9999	0.9996
sigma_u	Coef.	5.10	4.07	4.5
	95% CI	(2.26–10.87)	(1.63–8.48)	(1.88–9.49)
Goodness of fit and other statistics				
Number of observations		502	502	502
DIC		216.0	221.6	231.4
ICC		0.8444	0.7757	0.812

CI credibility interval, OR odds ratio, ICC Intraclass correlation coefficient, Prob probability of direction, SSS social security system

the cost-effectiveness plane coincided with the findings in published cost-effectiveness analyses, that is, a majority of results were located in the north-east quadrant [5]. When we compared the foreign and the Spanish results, a majority of cases (92–93%) showed concordance in the decisions based on the thresholds of €25,000–€35,000 per QALY [7, 8, 95].

As stated in the introduction, this study follows and updates the study by Barbieri et al. [16], although the methods are not exactly the same. Barbieri et al. defined similarity in ICERs across countries as a difference of less than two-fold and found only 27% concordance (12 out of 44 comparisons) [16]. In contrast, our study found a much higher level of concordance, with 92–93% of cases showing coincident results. Beyond the differences in measures and methods between our study and that of Barbieri et al. (Barbieri et al. had to include 17 single-country studies to increase their sample), we managed to get a much larger number of comparisons, mainly due to the longer search period.

In the multilevel logistic regression, the factors that most affected the concordances between foreign and Spanish results, which acted as a proxy of generalizability, were the geographical variables ‘Eurozone’, ‘UK’, ‘France’, ‘Germany’ and ‘Italy’. For instance, when the foreign country was a member of the Eurozone, the probability of concordance in decisions between the Spanish and the foreign studies would be eight times the probability of those cases where the country is not within the Eurozone. To this effect, one must also account for the country-specific effects in countries such as France, Germany or Italy. Although it does not belong to the Eurozone, the concordances with the United Kingdom are also high. Interestingly, the results were slightly different when we used other thresholds, but the

Eurozone and United Kingdom were always relevant factors. This could be explained by the pricing policy in Spain where the price of drugs is decided based on several criteria and data, including the market price in other European countries [9]. It is interesting that Eurozone, that represents a group of countries with the same currency, has globally more effect than the type of healthcare system (SSS), for example.

In addition to the geographical concordances, the analysis also allows us to observe how the probability of concordance was higher when the technology was a drug and when the study was privately funded (only for a threshold of €25,000 per QALY).

On the negative side, the probability of concordance decreases when the analysed studies are older (only when applying a €25,000/QALY threshold), when Markov models are used for the analysis, and for specific disease types—namely digestive diseases in the model with a €30,000 threshold and circulatory diseases in the model with a €25,000 threshold. The only variable showing a negative effect on the probability of concordance across all models is when the comparator is not another treatment (i.e. when it is a placebo or no treatment). This result is consistent with the Spanish Guideline for the economic evaluation of medicines [27], where it is stated that the intervention will be compared with standard practice.

The analysis of the distance between incremental costs and incremental QALYs in Spain and foreign countries allowed us to observe that agreement in decision making is driven more by alignment in incremental QALY estimates than by alignment in incremental cost estimates, since the variables identified as relevant for explaining the distances in QALYs coincide with those found in the concordance analysis. For instance, the high level of concordance observed

Table 4 Coefficients of the predictors of dependent variables 'distance of incremental cost', in percentage and 'distance of incremental effectiveness', in percentage

Variable	Estimate	Dependent variable	
		dist%_cost	dist%_effect
UK	exp[Coef]	1.47	1.18
	95% CI	(0.98–2.21)	(0.69–2.05)
	Prob	0.9681	0.7234
France	exp[Coef]	1.23	0.59
	95% CI	(0.79–1.92)	(0.32–1.07)
	Prob	0.8158	0.9569
Germany	exp[Coef]	1.56	0.65
	95% CI	(1.03–2.38)	(0.37–1.16)
	Prob	0.9827	0.9283
Italy	exp[Coef]	0.73	0.57
	95% CI	(0.49–1.11)	(0.33–0.98)
	Prob	0.9303	0.979
Eurozone	exp[Coef]	1.05	0.59
	95% CI	(0.74–1.5)	(0.36–0.95)
	Prob	0.6185	0.9857
SSS	exp[Coef]	0.9	1.43
	95% CI	(0.63–1.29)	(0.88–2.32)
	Prob	0.714	0.9229
Circulatory_disease	exp[Coef]	0.55	0.38
	95% CI	(0.28–1.06)	(0.11–1.47)
	Prob	0.9622	0.9242
Digestive_disease	exp[Coef]	0.74	0.03
	95% CI	(0.22–2.67)	(0–0.37)
	Prob	0.6939	0.9963
Cancer	exp[Coef]	0.61	0.89
	95% CI	(0.24–1.52)	(0.16–5.62)
	Prob	0.8583	0.5586
Drug	exp[Coef]	0.64	1.11
	95% CI	(0.32–1.31)	(0.29–4.11)
	Prob	0.8982	0.5738
Vaccine	exp[Coef]	1.66	20.76
	95% CI	(0.18–15.66)	(0.33–1601.99)
	Prob	0.6734	0.921
Comparator_notreatment	exp[Coef]	0.78	1.97
	95% CI	(0.39–1.58)	(0.5–7.46)
	Prob	0.7712	0.8435
Markov	exp[Coef]	0.63	0.95
	95% CI	(0.33–1.2)	(0.27–3.37)
	Prob	0.9227	0.5367
Horizon_0_5	exp[Coef]	1.32	0.83
	95% CI	(0.61–2.96)	(0.17–3.67)
	Prob	0.7516	0.593
Only_DMC	exp[Coef]	0.74	0.39
	95% CI	(0.32–1.66)	(0.09–2.01)
	Prob	0.7644	0.8883
Years_old	exp[Coef]	1.07	1.1
	95% CI	(1–1.13)	(0.99–1.24)
	Prob	0.9804	0.9568

Table 4 (continued)

Variable	Estimate	Dependent variable	
		dist%_cost	dist%_effect
Private_funds	exp[Coef]	1.32	1.7
	95% CI	(0.56–2.96)	(0.33–8.04)
	Prob	0.753	0.7411
Cons	Coef	4.21	1.26
	95% CI	(3.08–5.37)	(–0.89 to 3.33)
	Prob	>0.9999	0.8993
sigma_u	Coef.	0.83	1.78
	95% CI	(0.61–1.09)	(1.38–2.28)
Goodness of fit and other statistics			
Number of observations		418	418
DIC		1240.0	1490.0

CI credibility interval, ICC Intraclass correlation coefficient, Prob probability of direction, SSS social security system

in countries such as France, Italy and generally within the Eurozone is attributable to similar estimates of incremental QALYs. Similarly, older studies exhibited larger discrepancies in both estimated incremental costs and incremental QALYs.

This study had some limitations and some strengths. Among the limitations, firstly, we used as definition of generalizability a specific dimension of this broad term. We simplified our definition of generalizability to the concordance in the decisions based on the comparison of ICERs and cost-effectiveness thresholds between countries. This definition could be limited but we believe it provides a valuable—albeit simplified—proxy to explore the potential generalizability of economic evaluations across countries.

We recognize that the use of cost-effectiveness evidence in each country is different. Cost utility is used for decisions about the reimbursement of medicines in Sweden or the United Kingdom and for the negotiation of prices in France, while Germany does not use a cost-effectiveness threshold for decision making [96–98]. In Spain, cost-effectiveness information is considered when making decisions, although its exact role is not explicit and the threshold is not explicit [9]. There is currently a debate in Spain (and forthcoming legislation) that could change this and make it difficult to predict how valuable our results will be in the long term.

Secondly, as this was conducted as a scoping review, we did not assess the quality of the selected studies or their compliance with national cost-effectiveness guidelines. While we assumed that peer-reviewed multinational economic evaluations would adhere to minimum methodological standards, we acknowledge that variations in quality could influence the interpretation of generalizability. Consequently, an important limitation of this study is that the methodological quality of the individual studies was neither

formally assessed nor included as a factor in the statistical analysis.

While adherence to national guidelines is a necessary condition for a study to be considered generalizable, our analysis is limited. However, we consider that only a few studies included in our review would be entirely ruled out from such an assessment based on their external validity in the Spanish context. Spanish guidelines for economic evaluations [23, 27, 28] consist of recommendations, not mandatory requirements, and allow for a certain degree of flexibility in several criteria—similar to guidelines in other countries [30, 99]. The recommended type of study and health outcome measure (cost-utility analysis and quality-adjusted life years, respectively) were both required criteria for inclusion in our review. Moreover, almost all studies in our review conducted the analysis from the perspectives recommended in Spain (healthcare system and societal perspectives) and included sensitivity analyses. Most of them also fulfilled the recommendations on time horizon, with the majority of studies modelling lifetime costs and effects or using a long enough horizon appropriate to the disease. One of the major concerns is the selection of the comparator (Spanish guidelines recommend considering usual care), as it may vary substantially between countries. A consistent finding of our study is that those analyses using a placebo or no-treatment comparator have a lower probability of matching the Spanish case. Finally, in our review, 47% of studies reported following economic evaluation guidelines (typically when justifying the national discount rates), 58% used the rate recommended in Spain (3%), 21% used a close rate (3.5%) [100, 101], while only 9% used an outdated rate (6%).

Thirdly, the external validity of the analysis is limited as it was conducted from the point of view of a specific country. Nevertheless, this was designed on purpose as

generalizability is not an absolute concept and decisions are always made from the point of view of a specific entity [12].

Fourthly, there is some risk of selection bias as only multinational studies were included and almost 100% of included studies were model-based economic evaluations of medicines, conducted in high-income countries. Consequently, generalizability of results to middle and low-income settings is limited. In addition, the sample may not fully represent single-country studies or those focusing on less commonly evaluated technologies (on the other hand, as all of them were multinational studies whose methods and/or models were the same within each study for all countries, only differences in the country-specific data used by authors affected the differences in cost-effectiveness results).

There is also a potential risk of publication bias as most included studies were funded or sponsored by pharmaceutical companies. It is known that studies with positive results are more likely to be published than those with negative results [102]. Moreover, pharmaceutical companies are the most interested party in the development of global economic models to be adapted to several countries for fulfilling requirements for HTA and reimbursement policies [103, 104]. Nevertheless, 40% of the studies included in our review found results in different quadrants of the cost-effectiveness plane in at least two countries, so the publication bias, if it exists, is not spread among all the studies included in our review.

When country-specific economic evaluations of health technologies are not feasible due to time or resource constraints, assessing the generalizability of foreign economic evaluations offers a valuable alternative to support informed decision making. Moreover, our approach may also be useful to check the robustness of the findings of a specific country or inform whether an economic evaluation should be prioritized. In any case, decision makers should consider the need to request cost-effectiveness studies from the sponsors/manufacturers or to conduct their own independent country-specific economic evaluations whenever possible, in addition to including in their appraisals other criteria such as clinical effectiveness, safety or public health reasons, to cite some of those mentioned in the law.

In the future, it would be interesting to replicate this study using real funding decisions made by authorities or cost-effectiveness results provided by HTA agencies. This approach would allow us to adopt a broader definition of generalizability—one that includes related concepts such as applicability and transferability. At present, this information is not publicly accessible in Spain.

Moreover, following Barbieri et al. [16], our scoping review was limited to multinational studies that included Spain. However, it would also be valuable to examine published economic evaluations—addressing the same research

question (population, intervention, comparator)—that are not constrained to multinational designs, that is, where methodological variables are less homogeneous. In such an alternative analysis, we would not expect as high a level of concordance as observed in the current study, but we could better explore variability in factors between comparisons—not only across studies.

This is the first study to closely align with the objective set out by Barbieri et al. in 2005 [16]. Revisiting the topic of generalizability was timely, given the progress made in standardizing economic evaluations of health technologies across countries [105], and the fact that many current national guidelines now explicitly address and provide recommendations on transferability [21].

In the study from Barbieri et al. [16], economic evaluations of medicines conducted in two or more Western European countries were reviewed to analyse differences in results between countries, as well as in decisions based on varying cost-effectiveness thresholds for a QALY. Our study provides an original empirical approach to explore the generalizability through both a concordance analysis of decisions and a complementary examination of relative differences in incremental costs and outcomes.

Barbieri et al. concluded that cost-effectiveness thresholds were a critical factor due to substantial cross-country variation in cost-effectiveness estimates [16]. Building on their work, we conducted sensitivity analyses to examine how different thresholds influenced conclusions.

5 Conclusions

Our study concludes that foreign cost-effectiveness results, particularly those from Eurozone countries (such as France, Germany, Italy) and the United Kingdom can often be generalizable and provide meaningful insights for decision making in Spain. However, this should not be interpreted as a reason to avoid the generation of country-specific cost-effectiveness evidence and/or the critical assessment of the transferability of foreign studies. Our conclusions are limited to evaluations of drugs. Further research is needed to confirm these findings and to assess whether similar generalizability applies to non-drug health technologies.

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Declarations

Conflict of interest None.

Data availability Relevant data is recorded in the electronic supplementary material.

Author contributions Lidia García-Pérez generated the research idea and wrote the first draft of the manuscript. Lidia García-Pérez and Miguel Ángel Negrín-Hernández systematically reviewed and extracted the relevant articles. Lidia García-Pérez, Miguel Ángel Negrín-Hernández and Ignacio Abásolo-Alessón performed the statistical analysis and interpretation of the results. All authors contributed substantially to the development of the final manuscript, reviewed its content critically and approved the final version for submission.

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