

Cost-Effectiveness Analysis of Renalof[®] versus Extracorporeal Shockwave Lithotripsy (ESWL) for the Treatment of Kidney Stones ≤ 1 cm in Nicaragua

Mélida M. Aguilar Chamorro¹, Sergio Vargas Collado¹, Leslie Pérez Ruíz², David Márquez Soriano³, Jorge Luis Soriano García³

¹Clínica Senior, Managua, Nicaragua

²Centro de Inmunología Molecular, Havana, Cuba

³Catalysis S.L., Madrid, Spain

Email: david@catalysis.es

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Abstract

Objectives: To assess the efficiency in terms of cost-effectiveness (CE) of oral Renalof[®] treatment versus extracorporeal shockwave lithotripsy (ESWL) in the treatment of kidney stones ≤ 1 cm in Nicaragua. **Methods:** A cost-effectiveness economic evaluation was carried out based on the results obtained in the randomised, prospective, observational, single-blind, prospective, phase 2 clinical trial. Cost-effectiveness and the incremental cost-effectiveness ratio (ICER) were calculated. Economic data were obtained from the Economics Department of Clínica Senior in Managua, Nicaragua. The monetary cost was expressed in US dollars (USD). **Results:** Treatment with Renalof[®] yielded a CE of \$1,323.08/% remission, while ESWL was \$9,498.54/% remission. The ICER shows that, in order to achieve a high percentage of kidney stone remission with ESWL, an extra \$4,734.70 per patient must be invested. **Conclusions:** The use of Renalof[®] is shown to be a more cost-effective option than ESWL. It is recommended for the treatment of kidney stones ≤ 1 cm in size.

Keywords

Economic Evaluation, Pharmacoeconomics, Renalof[®], Extracorporeal Shockwave Lithotripsy, Kidney Stones

1. Introduction

The formation of kidney stones or nephrolithiasis is a common condition, with a

worldwide prevalence of more than 10% [1] and its incidence is increasing annually across the world [2] [3]. Approximately 5% - 12% of the population in industrialised countries experience a symptomatic episode before the age of 70, with a somewhat lower incidence in Asia (1% - 5%) [4].

The clinical signs of kidney stones include pain, infection or obstruction of the urinary tract, and they are also considered to be a risk factor for chronic kidney disease (CKD). Moreover, urolithiasis is responsible for 1 - 13 in 1,000 hospitalisations annually [5] [6]. The rate of recurrence is high, ranging from 10% - 20% in the first two years and 40% - 60% ten years after the first episode [7]. This is characterised by variable recurrences and morbidity, depending on the region studied [1]. Combined with the annual increase in this condition, this makes it a significant economic burden for both developing and developed nations [8].

Interventional procedures for the destruction and clearance of kidney stones, such as extracorporeal shockwave lithotripsy (ESWL), nephrolithotomy, and retrograde intra-renal surgery (RIRS), have virtually replaced open surgical methods [9] [10]. These techniques, while achieving a high percentage of stone clearance, can lead to intraoperative, postoperative, obstructive and infectious complications, which can in turn lead to hospitalisation and treatment of adverse events, thus increasing the cost of these procedures [11].

Therefore, there is a need for less invasive and safer medical treatments to treat the physiological, metabolic or physio-chemical abnormalities that affect stone formation and reduce recurrence. One of these treatment options is Renalof[®], the main ingredient of which is an extract of *Agropyrum repens* enhanced with Molecular Activation Technology (Catalysis S.L., Spain). The efficacy of this product was evaluated in a phase 2 clinical trial carried out in two health centres in Managua, Nicaragua, in which a kidney stone clearance rate of 65% and 97% was obtained at one and three months, respectively, and its use is therefore recommended in this type of patient [1].

For this product to be included in kidney stone management protocols, an economic evaluation of the drug is required. This evaluation is part of the broader discipline of Health Technology Assessment (HTA), which aims to select those options that are efficient and have the most positive health impact [12].

The aim of this analysis was to assess the cost-effectiveness of oral Renalof[®] treatment versus ESWL in subjects with a diagnosis of kidney stones ≤ 1 cm, in Nicaragua.

2. Methods

A full cost-effectiveness economic evaluation was conducted to evaluate the economic impact of the use of Renalof[®] in the treatment of subjects diagnosed with kidney stones ≤ 1 cm.

2.1. Study Population

The study population consisted of 235 subjects. 120 of these were enrolled in the

Renalof[®] treatment arm of the randomised, prospective, single-blind, phase 2 clinical trial conducted at the Hospital Universitario Antonio Lenin Fonseca and Clínica Seniors, Managua, Nicaragua, from August 2019 to July 2020 [1].

A search of the Nicaraguan literature on non-surgical management and/or the economic evaluation of nephrolithiasis was carried out, but no results were found. Nor was an adequate record found of the number of procedures to treat this condition that are performed each year in the country. Hence, in the case of the comparator group (ESWL), the efficacy data from a cohort of 115 subjects who underwent ESWL treatments from May 2014 to November 2021 at the Urology Clinic of the University of Sarajevo Clinical Centre were used [13].

2.2. Options

1. Renalof[®] 325 mg capsules (molecularly activated *Agropyrum repens* extract, mannitol, corn starch, talc) (Catalysis S.L., Spain).
2. Extracorporeal shockwave lithotripsy (ESWL).

2.3. Perspective and Timeframe

The perspective used was the Nicaraguan National Health System and the timeframe was three months.

2.4. Clinical Efficacy Variable

The primary variable was kidney stone clearance (% remission) with Renalof[®] or ESWL treatment, with evaluation at three months. For the Renalof[®] group this was obtained from the clinical study [1] and for ESWL, it was as per the findings in the retrospective cohort [13].

2.5. Cost Variables

Cost data were obtained from the Economics Department of Clínica Senior in Managua, Nicaragua. Direct healthcare costs (consultation, imaging, laboratory tests, concomitant treatment, hospitalisation and treatment) were considered in the economic evaluation. Each of these was calculated, using the formulas below. The currency used was the US dollar (USD) at 2023 prices.

2.5.1. Consultation Costs

The cost for urology consultation (UC) was calculated as follows:

$$(1) \text{ UC} = \text{UC UNIT COST} \times \text{NC}$$

Where: UC UNIT COST, per-unit cost of urology consultation; NC, number of consultations per patient. UC UNIT COST = \$40, NC = 3 consultations per patient (baseline, week 6 and week 12).

2.5.2. Imaging Costs

The cost per imaging test (CPI) was determined as follows:

$$(2) \text{ CPI} = (\text{RV UTS UNIT COST} \times \text{NT}) + (\text{AB CT UNIT COST} \times \text{NT})$$

Where: RV UTS UNIT COST, per unit cost of renovesical ultrasound; AB CT

UNIT COST, per unit cost of abdominal CT; NT, number of times each examination was performed per patient.

RV UTS UNIT COST = \$35, AB CT UNIT COST = \$250, NT UTS = 2 and NT CT = 1.

2.5.3. Laboratory Test Costs

The cost per laboratory examination (CLE) was calculated using the formula:

$$(3) \quad \text{CLE} = (\text{CBC UNIT COST} + \text{CR UNIT COST} + \text{UC UNIT COST} + \text{UA UNIT COST} + \text{GUT UNIT COST}) \times \text{NM}$$

Where: CBC UNIT COST, per unit cost of complete blood count; CR UNIT COST, per unit cost of creatinine; UC UNIT COST, per unit cost of urine culture; UA UNIT COST, per unit cost of uric acid; GUT UNIT COST, per unit cost of general urine test; NM, number of measurements of each test performed for each patient.

CBC UNIT COST = \$7, CR UNIT COST = \$7, UC UNIT COST = \$15, UA UNIT COST = \$7, GUT UNIT COST = \$10 and NM = 2.

2.5.4. Concomitant Treatment Costs

A worst-case scenario was assumed where a patient requires the full battery of concomitant treatments. The cost per concomitant treatment (CCT) was calculated using the formula:

$$(4) \quad \text{CCT} = (\text{AC UNIT COST} \times \text{NC}) + (\text{UA UNIT COST} \times \text{NM}) + (\text{IM UNIT COST} \times \text{NM}) + (\text{AP UNIT COST})$$

Where: AC UNIT COST, per unit cost of antibiotic cycle; NC, number of cycles; UA UNIT COST, per unit cost of urinary antiseptic; NM, number of months; IM UNIT COST, per unit cost of immunomodulator; AP UNIT COST, per unit cost of antipyretic;

AC UNIT COST for 14 days = \$50 and NC = 1 (one cycle per patient was selected, because the observed behaviour is that 80% of patients only require one cycle). UA UNIT COST for 1 month = \$60, IM UNIT COST for 1 month = \$35, NM = 3, AP UNIT COST = \$10.

2.5.5. Hospitalisation Costs (HC)

This cost only applies to the ESWL treatment group. Considering that a successful outcome results in an average hospital stay of two days, with costs varying from \$1,000 to \$1,300, the most expensive scenario (\$1,300) was selected.

2.5.6. Treatment Costs

Renalof[®] treatment costs (RTC)

Treatment regimen: Dose: 1 capsule of Renalof[®] 325 mg every 8 hours (3 capsules per day), for 3 months. One bottle of Renalof[®] contains 30 capsules and assuming 1 month = 30 days, in one month a patient consumes 90 capsules (3 bottles of Renalof[®]), thus three months would be 9 bottles of Renalof[®]. One 30-capsule bottle of Renalof[®] = \$22 (citation). Treatment for one patient for 3 months = \$198.

The cost of ESWL in Nicaragua for one patient = \$3,000. According to the published article on the cohort of patients studied, the mean number of sessions performed for kidney stone clearance was 1.70 ± 1.36 [13]. Therefore, an assumption of 2 sessions per patient was used. The calculation used the following equation:

$$(5) \text{ LTC} = \text{ESWL UNIT COST} \times \text{NS}$$

Where: ESWL UNIT COST, per-unit cost of ESWL; NS, number of sessions.

2.5.7. Total Cost

The total cost per patient for each of the options evaluated was determined by adding up each cost item, using the formulas:

$$(6) \text{ Cost of Renalof}^{\text{®}} \text{ Option (CRO)} = \text{UC} + \text{CPI} + \text{CLE} + \text{CCT} + \text{RTC}$$

$$(7) \text{ Cost of ESWL Option (CESWLO)} = \text{UC} + \text{CPI} + \text{CCT} + \text{HC} + \text{LTC}$$

To calculate the total cost of the sample in each case, for the Renalof[®] option, the result of equation 6 was multiplied by 120; and for ESWL, the result of equation 7 was multiplied by 115.

2.6. Cost-Effectiveness Analysis

The key parameters of the cost-effectiveness analysis used in the economic evaluation were the cost-effectiveness (CE) and the incremental cost-effectiveness ratio (ICER).

The CE for each treatment option was obtained by dividing the cost (C) by the effectiveness expressed as a percentage of remission (E) for each option ($\text{CE} = \text{C}/\text{E}$). The value of each CE was compared and the most efficient option, the dominated option (produces worse outcomes than most alternatives with higher costs) and the dominant option (produces better health outcomes with lower associated costs) were selected. CE was expressed with the indicator USD/% remission.

The incremental cost (difference between the costs for each option, $\Delta\text{C} = \text{C}_2 - \text{C}_1$) and the incremental effectiveness (difference between the effectiveness of each treatment, $\Delta\text{E} = \text{E}_2 - \text{E}_1$) were calculated. Using these differences, the ICER was calculated by dividing the incremental cost by the incremental effectiveness ($\Delta\text{C}/\Delta\text{E}$).

$$(8) \text{ ICER} = \frac{\text{C}_2 - \text{C}_1}{\text{E}_2 - \text{E}_1}$$

Where: C_2 , cost of the most expensive option; C_1 , cost of the least expensive option; E_2 , effectiveness of the most expensive option; E_1 , effectiveness of the least expensive option.

The ICER was expressed as the additional monetary units needed to gain the best percentage of kidney stone clearance per patient (USD/% additional remission).

2.7. Decision Rule

Since Nicaragua does not have a Health Technology Assessment Unit, nor an established decision threshold for deciding whether the technologies assessed are

cost-effective, [14] the World Health Organization's Choosing Interventions that are Cost-Effective (WHO-CHOICE) criterion, for countries that do not have an established decision threshold, was used as the decision rule in this analysis [15] [16].

According to this criterion, the ICER value is compared to the country's per capita gross domestic product (GDP) (latest available value in the literature is for 2022, \$2,255.40) [17]. If the ICER value is below the per capita GDP, the technology assessed is considered to be very cost-effective; if it is between 2 - 3 times [the GDP] it is cost-effective, and if it is over 3 times it is not cost-effective.

2.8. Sensitivity Analysis (SA)

A deterministic univariate and bivariate SA was performed [18] [19]. The worst-case (minimum efficacy and highest cost) and best-case (minimum cost and maximum efficacy) scenarios were analysed. Changes were made to the cost and efficacy variables for each option analysed. Variations of $\pm 10\%$ and $\pm 5\%$ with respect to the base case (BC) result were used for each variable, as per Mexico's economic evaluation guidelines [20]. An ICER value was obtained for each variation and a tornado chart was produced.

3. Results

In the CE, 97.5% kidney stone remission was achieved in the Renalof[®] group at the third and final visit (at 12 weeks) [1]. In the cohort of subjects taken from the literature for the ESWL group, in patients with stone size ≤ 10 mm, 99% remission was achieved at week 12 [13].

Table 1 shows the costs broken down by line items, total costs and average costs per treatment option.

Table 1. Total and average costs broken down by item, per treatment option*.

Cost items per treatment option	Average cost of each option per item (USD)	Total cost of each option per item (USD)	Total cost of each item (USD)
Consultation			
ESWL	120.00	13,800.00	28,200.00
Renalof [®]	120.00	14,400.00	
Imaging			
ESWL	320.00	36,800.00	75,200.00
Renalof [®]	320.00	38,400.00	
Laboratory Tests			
ESWL	92.00	10,580.00	21,620.00
Renalof [®]	92.00	11,040.00	
Concomitant treatment			
ESWL	345.00	39,675.00	81,075.00
Renalof [®]	345.00	41,400.00	

Continued

Hospitalisation			
ESWL	1,300.00	149,500.00	149,500.00
Renalof [®]	0	00.00	
Treatment			
ESWL	6,000.00	690,000.00	713,760.00
Renalof [®]	198.00	23,760.00	

*ESWL n = 115, Renalof[®] n = 120. ESWL, extracorporeal shockwave lithotripsy; USD, US dollars.

The largest cost item was treatment, with a value of \$713,760.00 (96.7% due to ESWL and only 3.3% for Renalof[®]). On the other hand, the lowest cost item was laboratory tests, with a value of \$21,620.00. The percentage contribution of each item per treatment option is shown below in **Figure 1**.

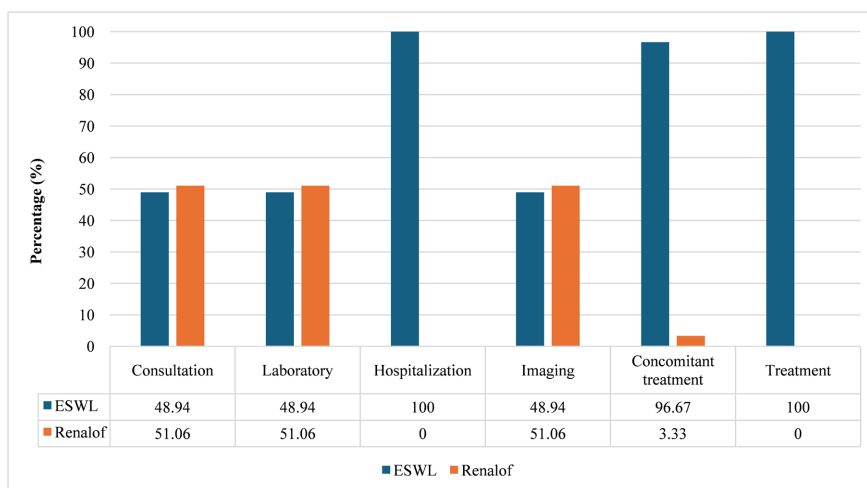


Figure 1. Percentage contribution of each item per treatment option.

ESWL, extracorporeal shockwave lithotripsy.

The most expensive option was ESWL with a total cost of \$940,355.00 and an average cost of \$8,177 per patient. The Renalof[®] option had a total cost of \$129,000.00 and an average cost of \$1,075 per patient.

When comparing both options with respect to their cost-effectiveness ratio, it was found that the most efficient option was Renalof[®], with \$1,323.08/% remission vs. ESWL with \$9,498.54/% remission.

The ICER value was an additional \$4,734.70 [8,177(C2) - 1075(C1) = 7,102/99(E2) - 97.5 (E1) = 1.5] per % remission per patient, which means that for each remission of a patient with kidney stones ≤10 mm, the Nicaraguan National Health System (NHS) would have to cover an additional cost of \$4,734.70 per patient in the case of the ESWL option.

When comparing the ICER value obtained, it was 2.1 times the country's per capita GDP (\$2,255.40) [12]. Therefore, the ESWL option was deemed cost-effective

for widespread use in the NHS, in accordance with the established decision rule.

The results of the deterministic SA are shown in **Table 2**.

Table 2. Cost difference, effectiveness difference and ICER of Renalof® vs. ESWL. Deterministic Sensitivity Analysis

Scenario	Variation (%)		ΔC (USD)	ΔE (% remission)	ICER (USD/% remission)	
	Cost	Effectiveness				
UNIVARIATE SA	1	BC	-5	7,102.00	1.43	4,983.86
	2	BC	5	7,102.00	1.58	4,509.21
	3	BC	-10	7,102.00	1.35	5,260.74
	4	BC	10	7,102.00	1.65	4,304.24
	5	-5	BC	6,746.90	1.50	4,497.93
	6	5	BC	7,457.10	1.50	4,971.40
	7	-10	BC	6,391.80	1.50	4,261.20
	8	10	BC	7,812.20	1.50	5,208.13
MULTIVARIATE SA	9	-5	-5	6,746.90	1.43	4,734.67
	10	-5	5	6,746.90	1.58	4,283.75
	11	5	-5	7,457.10	1.43	5,233.05
	12	5	5	7,457.10	1.58	4,734.67
	13	-10	-10	6,391.80	1.35	4,734.67
	14	-10	10	6,391.80	1.65	3,873.82
	15	10	-10	7,812.20	1.35	5,786.81
	16	10	10	7,812.20	1.65	4,734.67
	17	-5	-10	6,746.90	1.35	4,997.70
	18	-5	10	6,746.90	1.65	4,089.03
	19	5	-10	7,457.10	1.35	5,523.78
	20	5	10	7,457.10	1.65	4,519.45
	21	-10	-5	6,391.80	1.43	4,485.47
	22	-10	5	6,391.80	1.58	4,058.29
	23	10	-5	7,812.20	1.43	5,482.25
	24	10	5	7,812.20	1.58	4,960.13

SA, sensitivity analysis; ΔC , cost difference; ΔE , effectiveness difference; ICER, incremental cost-effectiveness ratio; BC, base case; ESWL, extracorporeal shockwave lithotripsy.

As can be seen in the table above, in all scenarios the ESWL option was found to be cost-effective, with a similar result to the base case, although it remains the case that in most scenarios the ICER is 2 to 3 times higher than Nicaragua's per capita GDP.

The tornado chart in **Figure 2** shows that the ICER values obtained were sensitive to the greatest variations used ($\pm 10\%$). Therefore, it should be noted that

greater attention should be paid to larger variations than those used here, to reduce their uncertainty and their effect on the results.

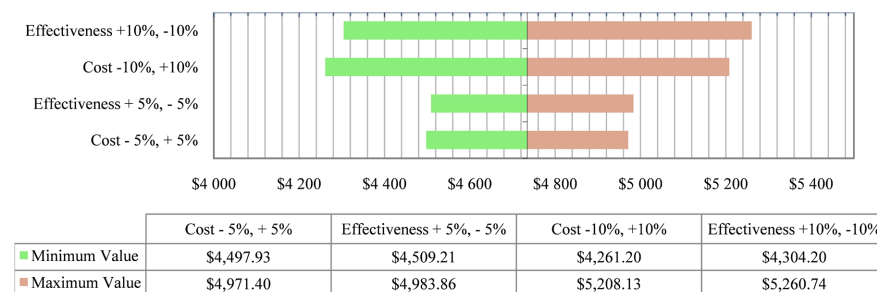


Figure 2. Tornado chart of results of deterministic SA to assess the influence of the parameters on the ICER.

4. Discussion

Urolithiasis is the third most common urological condition and a major cause of morbidity in 10% - 15% of people worldwide. Changes in diet and lifestyle will result in a projected increase of almost 2 million cases by 2050, with a 25% increase in health care costs [21].

Kidney stones ≤ 10 mm account for 60% - 65% of all urinary tract calculi, and when these are located in the renal collecting system or proximal ureter, ESWL is a reasonable first choice. For those located in the middle and distal portions, endoscopic techniques are usually the treatment of choice, although ESWL could be considered as a treatment alternative [22].

The ESWL option used in this study reports 99% efficacy for the group of patients with kidney stones ≤ 10 mm (best-case efficacy scenario) [13]. Pace *et al.* reported a low success rate of re-treatment with ESWL after initial failure, as out of 1,588 patients, 68% had remission after one session, 46% after the second and 31% after the third treatment, for an overall remission rate of 77% after the final session [23].

A meta-analysis of 1,607 patients reported an overall remission rate of 73% for ESWL for distal ureteral calculi [24], while in Türkiye, a study of 2,836 patients reported a success rate of 88.4% for all distal ureteral calculi, with 90.4% for those smaller than 10 mm [25].

In studies by Martov *et al.*, and Kristyantoro *et al.*, treatment with Renalof[®] significantly decreased stone size and stone clearance rate [26] [27]. Renalof[®] achieved a 97.5% remission rate, according to the clinical trial used for this analysis. This result is higher than that reported by Atiéti *et al.*, where an 86.5% response rate was achieved at month 3 [28].

Complications of ESWL in the treatment of lithiasis depend on many factors, including size, hardness, multiplicity and location of the stone, number, intensity and frequency of shockwaves administered, urinary tract conditions, presence or absence of urinary tract infection, use of antiplatelet drugs, anticoagulants, arterial hypertension and associated comorbidity, i.e. factors which are re-

lated to the patient, the stone, the urinary tract and the shockwave generating system [10] [29]. Infectious complications occur in 7.7% - 23% of cases, with sepsis being the most severe (1% - 2.7%), and those related to kidney stone fragments vary from 4% - 59%, including renal colic (2% - 4%), while haemorrhagic complications due to vascular damage include haematuria and subcapsular renal haematomas (4% - 19%) [10] [29] [30].

On the other hand, the Renalof[®] option has lower occurrence of residual kidney stones, which translates into a lower frequency of urinary tract infections, in less than 8% of patients. The most frequently reported adverse events are nausea, diarrhoea, and cramps. These events are classified as mild, disappear within the second week of treatment and generally do not lead to discontinuation of treatment [25]-[27]. In the clinical study used for this analysis, only 3.33% of patients reported drug-related adverse events (nausea) [1].

In this economic evaluation, the use of ESWL leads to an increase in the disease treatment costs, but it is a cost-effective option according to the CHOICE criterion, as it is under three times Nicaragua's annual per capita GDP [15] [16]. However, Renalof[®] offers a more efficient and dominant option, as it achieves high efficacy, similar to ESWL, at lower costs (\$1,075.00 vs. \$8,177.00 per patient), and represents an avoided cost of \$7,102.00 per patient.

In addition, the use of ESWL requires specialised personnel, equipment and admission of the patient for the procedure. It may also cause adverse events that could lead to hospitalisation and additional treatment, thus increasing the cost of this option [31]. Furthermore, although it has a higher efficacy (we used the study with the best-performance scenario for this variable as a comparator), because it has a higher probability of residual kidney stones, it would lead to a higher number of urinary tract infections [10] [29] and even other authors report retreatment rates of 42.6% [32].

In patients treated with Renalof[®] as monotherapy, without the use of another prescription, an improvement in quality of life is observed, since the average number of stones present in the urinary tract, episodes of renal colic, and extra-renal symptoms are ostensibly reduced, with a good safety profile [28]. As it is administered on an outpatient basis, it avoids the costs of hospitalisation and only entails the costs related to consultation and follow-up examinations (imaging, laboratory tests) on the days corresponding to the subject's assessment.

Therefore, the ESWL option (with limited availability in Nicaragua and other resource-limited countries), despite being classified as cost-effective, should be deemed a treatment strategy with a tiered and individualised priority, since, considering the discussion above, it would have a negative impact on the patient's and/or society's financial costs. An example of this is a study in England that estimated the initial cost of treating lithiasis at between £190 million and £324 million, comparable to the combined cost of initial treatment for bladder and prostate cancer UK-wide [33].

In terms of costs, with the use of Renalof[®] as a first-line strategy in the treatment of patients with kidney stones under 1 cm, the Nicaraguan NHS would

save \$710,200.00 for every 100 patients with this condition, and would leave ESWL as a second step for those who do not achieve remission. In another study, patients in the Renalof[®] group achieved a 1.5-fold reduction in stone density and a three-fold reduction in stone size versus the control group after only one month of treatment, and required fewer (two or more) sessions of ESWL (20.6% vs.49.4%) [34].

Given the deterministic sensitivity analysis shown in the tornado chart, it should be noted that greater attention should be paid to larger variations than those used here, to reduce their uncertainty and their effect on the results.

Limitations

The main limitation of the study was that it was based on retrospective sources of information, i.e. it was an economic analysis based on data obtained from studies completed in different contexts, which were not designed to include an economic evaluation. Therefore, information bias may be implicit in this study. This bias is due to the collection of the information needed for the research, especially when routinely collected data are used *a posteriori* for other purposes.

On the other hand, no clinical trials comparing both treatment options were found in the literature reviewed, and this required assumptions to be made in order to conduct the economic evaluation. In addition, because the study was conducted with retrospective information, some data concerning the resources used could not be obtained, for example, the costs of treating adverse events. In the absence of cost databases for the country's public health system, these were obtained from the cost records of the Economic Department of Clínica Senior in Managua, Nicaragua.

5. Conclusion

According to the results obtained in this economic evaluation, both options have similar efficacy and in the case of Renalof[®], it is a non-invasive, safe and less expensive treatment. Therefore, in view of the above, Renalof[®] is recommended for the treatment of small kidney stones, where high efficacy at reasonable costs has been observed. It is also recommended that Nicaraguan health policy-makers include this product in the management protocols for kidney stone disease. This would save the National Health System a significant amount of money in countries with similar situations, thus enabling reallocation of the system's limited resources to be used efficiently to meet unmet health needs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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