

# A prospective study of costs associated to the evaluation of nonsteroidal anti-inflammatory hypersensitivity reactions

To the editor,

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequent causes of drug hypersensitivity reactions, affecting 1%-3% of general population; the prevalence of NSAID hypersensitivity is higher in patients with chronic rhinosinusitis, nasal polyposis, asthma, or chronic urticaria, affecting up to 30% of patients<sup>1</sup>. The importance of its evaluation resides in the need of NSAIDs as analgesic/anti-inflammatory or antiplatelet therapy<sup>2</sup>.

This is a prospective, real-life, observational study aimed to evaluate all direct and indirect health costs of patients that consulted in our outpatient clinic for suspected NSAID hypersensitivity reactions. The study lasted from June 1, 2017, to May 31, 2018. The protocol was approved by the local Ethics Committee (code PI4505/2017) and all patients signed an informed written consent. Diagnostic procedures were carried out following the European Network of Drug Allergy/ European Academy of Allergy and Clinical Immunology (ENDA/EAACI) protocol<sup>3</sup>. Data concerning medication used for the study (consumption and costs) were collected in a structured way; data costs were provided by the Hospital Pharmacy Service (Table S1). Data about personnel, materials, and infrastructure costs were provided by the Bureau of Management of the Hospital (Table S2). Direct health costs were calculated considering the number of visits, complementary and diagnostic tests performed, and costs for personnel and materials used during the study. Direct nonhealth costs were calculated considering the number of travels and the distance in kilometers from patients' residences to the Allergy Service, applying the amount that the Spanish Authorities pay to public officials for the use of their private car and has been considered as locomotion expenses (€ 0.19 per kilometer)<sup>4</sup> (Figure S1). Indirect costs were based on loss of working hours (absenteeism). The average hourly labor cost in 2018 was estimated at € 27.4 in the European Union (EU)<sup>5</sup>. However, this average conceals significant differences between EU Member States. For more details about methods, see Appendix S1.

A total of 233 patients were evaluated. Of these, 212 (90.99%) completed the study. Mean age was  $50.99 \pm 17.56$  years. Median age was 52 and interquartile range 38-64 years. There was a predominance of females (67.38%). In 43 out of 233 patients (18.45%), hypersensitivity to NSAIDs was demonstrated. Regarding the type of reaction, in concordance with data published by Doña et al<sup>6</sup>, the number of anaphylaxis was appreciable (eight patients, 18.60%), 29 patients (67.44%) had had skin reactions (10 acute, 16 delayed and three unknown), and six respiratory symptoms (13.95%).

Cross-reactivity reactions were observed in 25 patients (58.14%), whereas 18 patients were single-drug reactors (Table 1).

Our results differentiated according to the EAACI classification phenotypes<sup>3</sup> are described in Appendix S1. We have confirmed such phenotypes in 13 patients that had positive challenge tests: 1 (7.69%) NERD, 1 (7.69%) SNIUAA, 7 (53.85%) NIUA, and 4 (30.77%) NIUAA.

In the global sample, the mean number of visits until a diagnosis was made was 3.50 (range 1-7). The mean number of visits up to completion of the diagnosis was greater in patients that had a final diagnosis of NSAID hypersensitivity ( $4.23 \pm 1.46$ ) than in patients that did not ( $3.34 \pm 1.42$ ) ( $P < .001$ ). There were no statistically significant differences in the mean number of visits between cross-reactive patients (NERD, NECD, and NIUA) ( $4.48 \pm 1.16$ ) and single-drug reactors (SNIUAA and SNIDR) ( $3.89 \pm 1.78$ ) ( $P = .140$ ).

In our study, the mean total cost per patient of an NSAID evaluation was €  $185.30 \pm 146.46$ , and it was distributed as follows: (a) direct health costs: € 104.87 (56.60%); (b) direct nonhealth costs: € 18.57 (10.02%) [total direct costs: € 123.44 (66.62%)]; (c) indirect costs: € 61.86 (33.38%) (Table 2).

Total costs per patient varied notably (minimum € 27.78; maximum € 1055.96) taking into account different variables (Figure S2). Those who had had acute reactions (84.55%) had an average total cost of €  $189.28 \pm 150.35$ , whereas those with delayed reactions (3.43%) was €  $189.45 \pm 142.01$  ( $P = .720$ ); in those whose reaction latency period was unknown (12.02%) was €  $160.84 \pm 121.23$ . Taking into account patients with or without a final diagnosis of hypersensitivity to NSAIDs, the average costs were €  $239.53 \pm 140.59$  and €  $173.02 \pm 145.71$ , respectively ( $P = .004$ ).

Particularly, the fact of being employed or not, significantly increased the cost (€ 304.10 vs € 114.93,  $P < .001$ ). For more details about results, see Appendix S1.

We have not found previous prospective studies addressing the costs of NSAID hypersensitivity evaluation. Blumenthal et al<sup>7</sup> prospectively studied outpatients with suspected beta-lactam allergy concluding that the costs of penicillin allergy evaluation reached \$ 220 for the base-case (with varied assumptions adjusting for operational challenges, clinical setting, and expanded testing could reach \$ 540). One of the advantages of performing a study of NSAID hypersensitivity is de-labeling of purported NSAID hypersensitivity patients. Being mislabeled as hypersensitivity to NSAIDs could lead patients to receive alternative drugs, clinically and economically less effective. Sastre et al<sup>8</sup> evaluated the medical and economic impact of a misdiagnosis of drug hypersensitivity in hospitalized patients (including 23

	Total patients N (%)	Cross-reactive patients N (%)	Single-drug reactors N (%)	P-value
<b>NSAID</b>				
Acetylsalicylic acid	10 (23.26)	10 (100)	0 (0)	<b>.002</b>
Metamizole	11 (25.58)	0 (0)	11 (100)	<b>&lt;.001</b>
Ibuprofen	11 (25.58)	8 (72.73)	3 (27.27)	.227
Dexibuprofen	1 (2.33)	1 (100)	0 (0)	1
Diclofenac	4 (9.30)	3 (75)	1 (25)	.625
Dexketoprofen	4 (9.30)	2 (50)	2 (50)	1
Ketorolac	1 (2.33)	1 (100)	0 (0)	1
Naproxen	1 (2.33)	1 (100)	0 (0)	1
<b>Clinical manifestations</b>				
Urticaria	19 (44.19)	11 (57.89)	8 (42.11)	.648
Angioedema	9 (20.93)	8 (88.89)	1 (11.11)	<b>.039</b>
Anaphylaxis	8 (18.60)	0 (0)	8 (100)	<b>.008</b>
Bronchospasm	5 (11.63)	5 (100)	0 (0)	.063
Rhinoconjunctivitis	1 (2.33)	1 (100)	0 (0)	1
Fixed drug eruption	1 (2.33)	0 (0)	1 (100)	1
<b>Diagnosis</b>				
Clinical history	20 (46.51)	16 (80)	4 (20)	<b>.012</b>
Skin tests	10 (25.58)	0 (0)	10 (100)	<b>.002</b>
Controlled exposure tests	13 (29.55)	10 (76.92)	3 (23.08)	.092
<b>Total</b>				
43 (100)	25 (58.13)	19 (44.18)	-	

**TABLE 1** Nonsteroidal anti-inflammatory drugs involved, clinical features, and diagnostic method in patients with a final diagnosis of NSAID hypersensitivity. Cross-reactive and single-drug reactor patients are considered

Significant differences between cross-reactive patients and single-drug reactor patients were observed in some aspects (*P*-value in bold font): for drugs, in patients with hypersensitivity to acetylsalicylic acid and metamizole; for clinical manifestations in angioedema and anaphylaxis and for diagnosis, in those detected by clinical history and skin tests.

**TABLE 2** Total costs and percentages disaggregated by items and types of costs

Item	n	Cost (%)	Type of cost	Total cost (%)	Average cost
Skin and patch tests	109	€ 135.97 (0.31)	Direct health costs	€24 434.78 (56.60)	€ 104.87
Challenge tests	193	€ 1295.08 (3.00)			
In vitro tests	33	€ 332.31 (0.77)			
Materials and infrastructure	233	€ 727.70 (1.69)			
Health personnel fees	233	€ 21 943.72 (50.83)			
Travel expenses	233	€ 4326.87 (10.02)	Direct nonhealth costs	€ 4326.87 (10.02)	€18.57
Loss of working days	233	€ 14412.40 (33.38)	Indirect health costs	€14 412.40 (33.38)	€61.86
Total				€43 174.05 (100)	€185.30

Total costs and percentages disaggregated by items and types of costs: skin and patch tests, challenge tests, materials and infrastructure and health personnel fees (direct health costs), travel expenses (direct nonhealth costs), loss of working days (indirect health costs), total cost and average cost of them.

patients (28%) with hypersensitivity to NSAIDs). They observed that the use of alternative drugs increased the mean treatment costs by 4-folds (range, 2-11; mean, €273.47 per day). Focusing on antiplatelet treatment, Cubero et al<sup>9</sup> observed that acetylsalicylic acid (ASA) was the option with the greatest supporting clinical evidence and lowest

cost for the treatment of ischemic heart disease. The annual cost of alternative drugs such as clopidogrel or triflusal was 1142.12% (218.13 vs € 17.64) and 662.76% (134.56 vs € 17.64), respectively, greater than the cost of ASA. So, the elective evaluation and de-labeling of NSAID hypersensitivity can be greatly cost-effective.

Our study has some limitations: estimation of costs were not made by act, there was a high number of unemployed patients, most patients went to the clinic by walk, and there are differences in incomes among the different countries of the EU<sup>5</sup>. All these factors could affect the total cost of the study. (For more details see Appendix S1.)

In summary, in this prospective and comprehensive study, in which direct and indirect health costs of evaluating NSAID hypersensitivity were prospectively considered in a systematic way, a complete study averaged € 185.30 per patient. We believe that this is an assumable figure, particularly taking into account the advantages of de-labeling patients of NSAID hypersensitivity.

### CONFLICTS OF INTEREST

The authors declare that they have no relevant conflicts of interest related to this manuscript.

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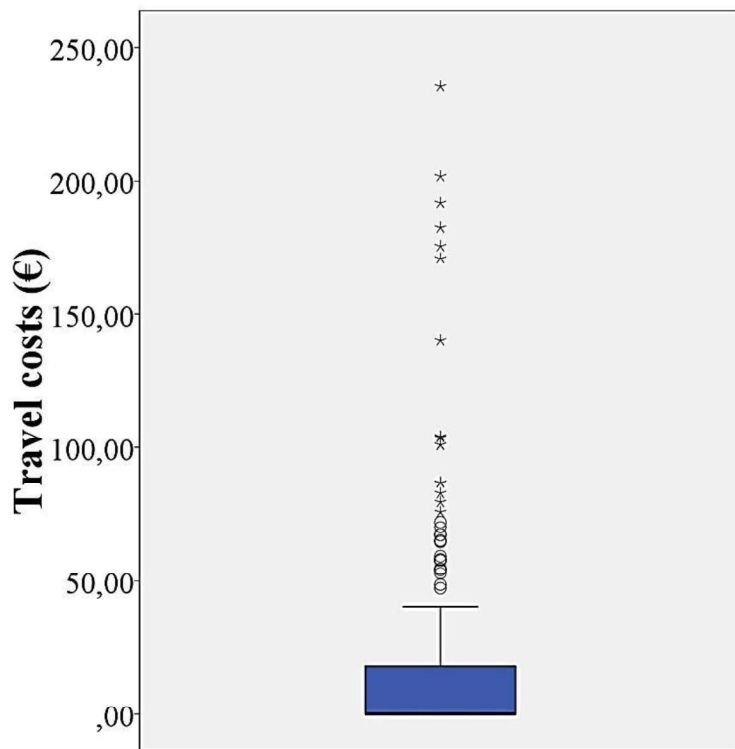
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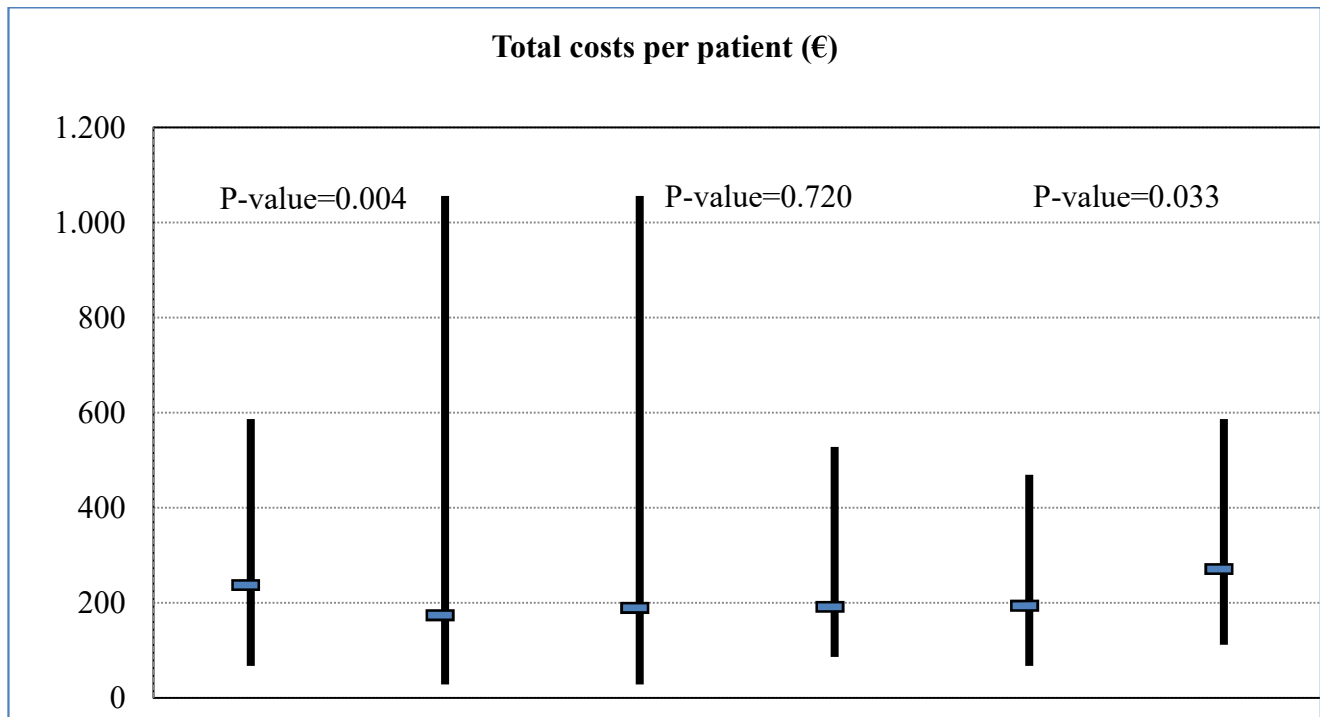
### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**Figure S1: Box-plot of the distribution of direct non-health costs (travel costs)**



**Figure S2. Total costs per patient (€) according to different variables**



	HS Patients	Non-HS Patients	Acute Reaction	Delayed Reaction	Single drug reactive patients	Cross reactive patients
Maximum cost	€586.77	€1,055.96	€1,055.96	€527.60	€469.68	€586.77
Average cost	€239.53	€173.02	€189.28	€189.45	€193.19	€272.89
Minimum cost	€66.94	€27.78	€27.78	€85.45	€66.94	€111.32

(†) HS: hypersensitivity

Total cost per patient (€) showing maximum, minimum and average cost according to different variables: hypersensitivity and non-hypersensitivity patients, acute and delayed reaction, single drug reactor and cross-reactive patients

**Table S1. Raw data of the study medication consumption costs provided by the Hospital Pharmacy Service**

ACTIVE PRINCIPLE	SPECIALTY	COST (€)
Acetylsalicylic acid	Adiro <sup>®</sup> 100 mg, tablets	0.56
Aceclofenac	Airtal <sup>®</sup> 100 mg, tablets	0.49
Diclofenac	Diclofenac 50 mg, tablets	0.34
Diclofenac	Voltaren <sup>®</sup> 75 mg/3 mL, amp.	5.40
Lornoxicam	Acabel <sup>®</sup> 4 mg, tablets	7.03
Meloxicam	Meloxicam 7.5 mg, tablets	5.20
Piroxicam	Feldene <sup>®</sup> 20 mg/1 mL, amp.	0.84
Dexketoprofen	Enantyum <sup>®</sup> 25 mg, tablets	1.12
Dexketoprofen	Enantyum <sup>®</sup> 50 mg/2 mL, amp.	2.30
Ketoprofen	Fastum <sup>®</sup> 50 mg, tablets	0.05
Ibuprofen	Pirofeno <sup>®</sup> 40 mg/mL, suspension	2.37
Ibuprofen	Ibuprofen 400 mg, tablets	0.04
Ibuprofen	Ibuprofen 600 mg, tablets	2.22
Ibuprofen	Ibuprofen (arginine) 400 mg, sachets	1.11
Naproxen	Naproxen 500 mg, tablets	0.31
Celecoxib	Celebrex <sup>®</sup> 200 mg, tablets	1.57
Etoricoxib	Arcoxia <sup>®</sup> 60 mg, tablets	75.76
Parecoxib	Dynastat <sup>®</sup> 40 mg, vial	5.96
Acetylsalicylic acid	Aspirin <sup>®</sup> 500 mg, tablets	16.18
Acetylsalicylic acid, ascorbic acid, codeine	Dolmen <sup>®</sup> tablets	0.29
Metamizole	Metamizole 2 g/5 mL, amp.	12.59
Metamizole	Metamizole 575 mg, tablets	1.18
Paracetamol	Dolocatil <sup>®</sup> 1 g, tablets	0.92
Paracetamol	Paracetamol 1 g/100 mL, solution	8.83
Paracetamol	Paracetamol 650 mg, tablets	0.48
Paracetamol, chlorpheniramine, dextromethorphan	Frenadol <sup>®</sup> , sachets	1.13
<b>TOTAL</b>		<b>154.27</b>

**Proportion of adults: 233/241**

**Adults medication consumption costs: (233/241)\*154.27= €149.15**

**Medical consumption costs because of a positive challenge test: €11.24**

**Total medication consumption costs: €160.39**

**Table S2. Consumption and payroll of the personal proportionally to the number of patients/visits (direct health costs)**

	Allergy Service		Patients of the study	
	Total cost (€) (y)	Number of annual visits (N)	Number of visits (n)	Total cost (€) (x)
Consumption	22,507.93	25,239	816	727.70
Personnel	678,722.63			21,943.72
<b>TOTAL</b>				<b>22,671.43</b>

The equation for attributing the total consumption and personnel costs to the patients of the study was:

$$x = \frac{y}{N} * n$$

Where:  $x$ : costs attributed to the patients of the study

$y$ : total costs attributed to all patients attended in the Allergy Service

$N$ : number of visits of all patients who were attended in the Allergy

Service

$n$ : number of visits of the patients of the study

## Appendix S1

### METHODS

This is a prospective observational study aimed to evaluate all patients of our outpatient clinic that consulted for suspected NSAID hypersensitivity reactions. The study lasted from the 1<sup>st</sup> June 2017 to the 31<sup>st</sup> May of the following year. The study protocol was approved by the local Ethics Committee (code PI4505/2017).

#### **Inclusion criteria**

All patients from the age of 14 years old that attended the Allergy outpatient clinic for suspected hypersensitivity reactions to NSAIDs in that time period were proposed to participate in the study. All patients who voluntarily agreed to participate in the study signed an informed written consent.

#### **Methodology of the evaluation of non-steroidal anti-inflammatory drug hypersensitivity reactions**

Diagnostic procedures were carried out following the European Network of Drug Allergy/ European Academy of Allergy and Clinical Immunology (ENDA/EAACI) protocol<sup>1</sup>. In addition to the anamnesis performed by the responsible physician, the protocol included the following procedures:

- In vivo tests

a) Skin prick test (SPT), intradermal and patch tests.

b) Single-blind, placebo-controlled exposure tests up to the therapeutic dose with different NSAIDs (Table S1).



We classified acute and delayed reactions following the Kowalski et al<sup>2</sup> algorithm, where they classify acute reactions as those occurring before 24 hours and delayed reactions as those occurring after 24 hours.

Usually, the clinical history was done in one visit and, when possible, the study was initiated. Then, the patient had further visits for skin testing and/or drug challenges. We administered placebo followed by the drug in increasing doses, until reaching the therapeutic dose. In patients with a positive result with a COX-1 inhibitor (acetylsalicylic acid) and depending on it, additional visits could be arranged for challenging with COX-2 inhibitors (for example, etoricoxib and/or meloxicam). All visits were prospectively recorded for each patient.

### **Data and variables collected**

For data collection, a structured questionnaire was handed out to all patients. Data obtained was stored in a dissociated database, so patients' anonymity was guaranteed.

### **Assessment of costs**

Data about personnel, materials and infrastructure costs were provided by the Bureau of Management of the University Hospital of Salamanca (Spain). Data concerning the medication used for the study (consumption and costs) were collected in a structured way; data costs were provided by the Hospital Pharmacy Service (Table S1).

To assess the costs in monetary terms, the following data were considered:

- Reagents used for skin testing and drugs used for challenge tests.
- Reagents used for laboratory tests.
- Fees of doctors, nurses, auxiliary health personnel and administrative staff.
- Building maintenance expenses (water, electricity, etc.).

- Patients transport to the consultation.
- Loss of working hours.

a) Direct health costs

Direct health costs were calculated taking into account the number of visits, the complementary and diagnostic tests performed, and costs for personnel and materials used during the study. All diagnostic tests were taken into account: *in vivo* tests (skin tests, patch tests and controlled drug exposure tests) and *in vitro* tests (tryptase levels). To estimate per patient costs derived from personnel fees, total costs were divided by the global number of visits of all the patients seen in the outpatient clinic during 2017. As in the Spanish National Health Service the remuneration of the staff does not depend on medical acts, it was assumed that the cost of each patient visit was the same. The total amount attributed to patients of the study, including personnel fees and building maintenance expenses, was proportionally calculated on the basis of the total amount attributed to the Allergy Service and the number of visits to the outpatient clinic during this period. This datum was provided by the Hospital Administration (Table S2).

b) Direct non-health costs

The direct non-health costs were calculated considering the number of travels and the distance in kilometers from their homes to the Allergy Service, estimating a cost of €0.19 per kilometer. This is the amount that the Spanish Authorities pay to public officials for the use of their private car and has been considered as locomotion costs<sup>3</sup>. The patients lived in the province of Salamanca that has 331,000 inhabitants. To attribute this cost to a single patient, the distance from the place of residence to the outpatient clinic was estimated. Patients living in the city of Salamanca, which is a

small town of 144,000 inhabitants located in the West of Spain, were considered going to the hospital by walk (most of them).

c) Indirect costs

Indirect costs were based on loss of working hours (absenteeism).

The average hourly labour cost in 2018 was estimated at €27.4 in the European Union (EU). However, this average masks significant differences between EU Member States, with hourly labour costs ranging between €5.4 in Bulgaria and €43.5 in Denmark<sup>4</sup>.

Gross earnings are the largest part of labour costs. Across EU Member States, the highest national median gross hourly earnings were 15 times higher than the lowest. Spain ranked number 13 of the 28 countries of the EU both in hourly labour costs as in median gross hourly earnings<sup>4</sup>.

If we take into account the differences in medical practice incomes among different countries of the UE the total mean cost would be different<sup>5</sup>. As example total the medical practice incomes in France, Germany and the UK are 79.25%, 135.85% and 144.34% higher, respectively. Consequently, the total mean costs would have been increased in €74.63, €127.94 and €135.94, respectively.

Costs generated in our patients in the year pervious to our study due to the fact of needing to attend Emergency room and/or its Primary Care Center as a consequence of the reaction presented.

We have estimated the costs caused by the patient the year before being studied due to drug adverse reactions. Taking into account the Decree 83/2013, of the Junta de Castilla y León<sup>6</sup>, obtained a total amount of €27,064.24, corresponding to 126 visits, [mean±standard deviation (SD): 0.54±0.88] to the Emergency Room (ER) and 198 visits, (0.85±0.84) to Primary Care. So the average expenditure per patient was €116.16.

If these patients would have not been studied, they maybe would have needed to go to the ER or their Primary Care again because of a new reaction.

### **Statistical analysis**

Data were analyzed using IBM<sup>®</sup> SPSS Statistics V25.0 (Armonk-IBM Corp., New York, USA) and it was considered a statistically significant result when  $p < 0.05$ . Quantitative variables were described by means and qualitative variables in terms of relative frequencies. Nonparametric test (Mann-Whitney test) and parametric test (T test independent samples) were used to compare quantitative variables.

## **RESULTS**

### **Direct health costs**

Total costs due to personnel and materials (maintenance expenses) used in the study reached €22,671.43. Of them, €727.70 corresponded to the cost of materials, whereas €21,943.72 corresponded to health care personnel costs (personnel expenses, including payroll and insurances) (Table S2).

The costs of skin tests (100 patients), patch tests (21 patients) were €135.97; and drug challenge tests (193 patients) and the costs of NSAID used in challenge tests were €1,295.08. Finally, total direct health care costs reached €24,434.78, with an average cost per patient of €104.87 (Table 2).

We had 13 patients with positive result in controlled exposure tests (30.23% of positive results). Of them, 7 patients (53.85%) did not required any medication and the other 6 (46.15%) did: 3 (23.08) antihistamines (dexchlorpheniramine or cetirizine) and corticosteroids (methylprednisolone). The other 3 patients (23.08%) resolved the symptoms with antihistamines (dexchlorpheniramine or cetirizine). These drugs

increased the costs of medication €11.24, so total medical consumption costs were €160.39 (Table S1). None of these patients required emergency care or intensive care. Nevertheless, in order to know the increase of costs if these cares would be necessary, we have made an estimation of these costs: €101.41 per Emergency Room visit, €408.74 per hospitalization day and €1,053.72 per day at Intensive Care Unit<sup>6</sup>.

Moreover, in 44 patients (18.89%) we evaluated other drugs taken at the same time as the index reaction. Of them, 34 antibiotics, 1 radiological contrast media and 9 other drugs, raising a total cost of €3,839.98.

A total of 217 patients (93.13%) initiated the study during the first visit. Of them, 40 patients (18.43%) finished the study at this first visit. The rest of patients had at least a second appointment where we started with the allergy study. The mean number of visits until a final diagnose was made was  $3.50 \pm 1.47$ . Skin tests were performed in 109 patients (46.78%). Of them, skin prick tests were performed in 100 patients, intradermal tests in 92 patients and patch tests in 21 patients. Delayed intradermal readings before challenge tests we performed in 8 patients (3.43%). Patients had had 197 acute reactions (84.55%), 8 delayed reactions (3.43%) and in 28 patients the latency period was unknown (12.02%).

We had 8 asthmatic patients, in which we performed a total of 24 spirometries. Considering a cost of €47.11 per each spirometry the total amount was €1,130.64. This cost is included in the item Challenge tests in Table 2.

Basal tryptase levels were performed in 33 patients that had had anaphylactic episodes, reaching a cost of €332.31. This cost is included in the item *In vitro* tests in Table 2.

### **Direct non-health costs**

The direct non-health costs were calculated considering the number of travels of patients and the kilometers from the different places of residence to the Allergy department. With an estimated cost of €0.19 per kilometer<sup>5</sup>, the global amount reached €4,326.87 (Table 2). Of the 233 patients studied, 102 came to our outpatient clinic from localities different to the hospital setting. As they were assumed to have come by car, the cost per kilometer was applied. The patient average number of kilometers traveled to attend all the consultations was 223.26 kilometers, with a per patient cost of €42.42. Data of travel expenses had a very asymmetrical distribution (Figure S1). Thus, average travel expenses, €18.57, were much influenced by a few high outliers.

### **Indirect health costs**

For calculating indirect health costs we considered the labor costs. This is due to the fact that in Spain when employees assist to medical consultation, they do not lose their salary. So, loss of income refers to labor costs lost by the employers. Logically, we found statistically significant differences ( $p$ -value $<0.001$ ) in the average total cost between working (€304.10 $\pm$ 172.55) and non-working patients (€114.93 $\pm$ 62.55).

Indirect health costs were calculated taking only into account work absenteeism. Total costs reached €14,412.40 (Table 2). The average income loss of the 233 studied patients was €61.86. Nevertheless, only 83 patients (35.62%) were employed; considering only employed patients, the average income loss was €173.64.

### **Total costs**

In summary, total costs were €43,174.05 for the global sample, with a mean a cost of €185.30 per patient (Table 2). Taking into account patients with or without a final

diagnosis of hypersensitivity to NSAIDs the average costs were €239.53±140.59 and €173.02±145.71, respectively (p=0.004). Finally, the average cost in single drug reactor patients (€193.19±122.90) and cross-reactive patients (€272.89±145.33) were significantly different (p=0.033) (Figure S2).

Medical costs were different according to the phenotype of NSAID hypersensitivity. We have calculated these costs in NERD and NECD patients comparing with NIUA and NIUAA and we have found that mean cost in NERD and NECD patients were €273.82±171.50 whereas in patients with NIUA and NIUAA were €250.76±94.87 (p=0.846).

Positive results in cross-reactive patients and single drug reactor patients following the EAACI classification phenotypes<sup>1</sup> are shown in the next table:

		N (%)	Concomitant atopy
Cross-reactive (non-immunological)	NERD	6 (13.95)	3 (50)
	NECD	4 (9.3)	0 (0)
	NIUA/NIUAA	15 (34.88)	2 (13.33)
<b>Total</b>		<b>25 (58.14)</b>	<b>5 (20)</b>
True drug allergy (immunological)	SNIUAA	17 (39.53)	6 (35.29)
	SNIDR	1 (2.33)	1 (100)
<b>Total</b>		<b>18 (41.86)</b>	<b>7 (38.89)</b>

*NERD*: NSAID-exacerbated respiratory disease

*NECD*: NSAID-exacerbated cutaneous disease

*NIUA/NIUAA*: NSAID-induced urticaria and/or angioedema

*SNIUAA*: NSAID-induced urticaria-angioedema and/or anaphylaxis

*SNIDR*: single NSAID-induced delayed reaction

## LIMITATIONS OF OUR STUDY

Our study has some limitations. We have made estimates according to the overall number of patients and not by act. This is due to the fact that in the public Spanish National Health Service payment to employees is not dependent of medical acts. In addition, although some estimates have been done considering the whole year 2017 and the studies lasted from June 2017 to May 2018, as the period is also of one year, we believe that the deviation is neglectable.

Regarding direct non-health costs, as we explained before, most of our patients went to the hospital by walk, due to the fact that Salamanca is small town of approximately 144,000 inhabitants. The rest of the patients living in the province of Salamanca were considered to have gone by car.

Another limitation of our study is the number of unemployed patients. We had a total of 58 patients (24.89%) under 16 years of over 65 years, so these patients are not employed, because at these ages, people do not usually work in Spain. It implies a lower mean global indirect cost in our study. However, this is due to the fact that our study is a real-life study. We also provide the costs in working patients notwithstanding.

Moreover, we must take into account that gross earnings at work are different between the different countries of EU<sup>4</sup>, which implies that the indirect costs are different from other countries. This also affects the total cost of the study.

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