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Clinical Factors Associated With Current Relevance in Allergic Contact Dermatitis: Development of Predictive Models Based on Data From the Spanish Contact Dermatitis Register (REIDAC)

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ABSTRACT

Background: Current relevance of positive patch-test reactions guides management in allergic contact dermatitis (ACD), yet its clinical predictors and the use of predictive models in clinical practice remain underused.

Objectives: To identify demographic and clinical factors associated with current relevance in ACD and to develop overall and allergen-specific predictive models.

Methods: A multicentric REIDAC study included data from patch-tested patients with the Spanish baseline series. Exposure history, anatomical sites, atopic status, and occupational data were recorded. Logistic regression (LR) models were trained and internally validated to predict current relevance overall and for top frequent allergens. Model discrimination was assessed with area under the receiver-operating characteristic curve (AUC).

Results: Among 17 005 patients, 4077 (24.0%) had at least one currently relevant reaction. The final overall LR model achieved an AUC for the validation sample of 0.679. Allergen-specific AUC parameters (LR) varied among allergens but performed best for nickel (AUC = 0.770). The independent factors associated with current relevance were female gender, specific body sites (hand, neck, head, leg, feet) and two occupations (hairdresser and construction workers). The use of other models (LASSO, gradient boosting) revealed similar results.

Conclusions: Prediction modelling may moderately predict current relevance in ACD and several clinical variables are associated with current relevance in ACD.

Leopoldo Borrego, Miguel Ángel Descalzo and Ana M. Giménez-Arnau contributed equally as senior authors and share last authorship.

For affiliations refer to page 8.

1 | Introduction

The diagnosis of allergic contact dermatitis (ACD) relies on patch testing [1]. The process of patch testing is complex and involves the study of patients' exposures and the detailed evaluation of relevance, if a positive result is found [1]. In this regard, assessing clinical relevance is crucial to determine whether a patient's dermatitis is explained by current exposure to any given substance(s) [2, 3]. Within the current classification of clinical relevance, the term 'current relevance' indicates that a specific allergen or product is responsible for the patient's current clinical presentation. In contrast, other types of relevance, such as 'past relevance' (where the allergen or product was responsible for symptoms in the past but is not currently causing symptoms) and 'unknown relevance' (where the clinical relevance cannot be determined), do not meet this criterion.

The study of current relevance is difficult in clinical practice, with variability among various publications and difficulty in evaluating trends. Furthermore, current relevance between different allergens may also present with significant variability [4, 5], as well as depend on the evaluations that are performed in the patient (e.g., in occupational dermatitis when workplace materials are also studied, a higher relevance of positive results may be detected) [6]. However, current relevance has emerged as a potential variable for predictive modelling in ACD [7, 8]. Despite a limited number of studies, previous investigations have been able to quantify a patient's likelihood of presenting a clinically relevant positive reaction in function of demographic and clinical parameters [7]. Furthermore, these studies have highlighted the need of further re-evaluating predictive accuracy of the models adding new parameters such as sites of involvement [7].

This study aims to evaluate the performance of predictive models for current clinical relevance based on clinical and demographic factors in a cohort of patients referred for patch testing. Furthermore, we also aim to perform these analyses for frequent allergens in the cohort.

2 | Methods

A prospective multicentric study of the data included from January 2019 to December 2024 in the Spanish Contact Dermatitis Register (REIDAC) was conducted. The REIDAC is a collaborative dermatology research network focused on ACD [9]. Patients were patch tested with the Spanish baseline. Allergens were commercially obtained from Chemotechnique (Vellinge, Sweden), allergEAZE or TrueTest, SmartPractice (Hillerød, Denmark), depending on the availability of each centre. Patch test performance, readings (days 2, 4 and variably, day 7), and reaction gradation were performed in accordance with the ESCD guidelines. As per guidelines, relevance was evaluated by trained dermatologists, after clinical examination and history of previous exposures, and graded accordingly (current, past, unknown) after patch testing or during follow-up after allergen avoidance. With regard to exposure identification, REIDAC centres will normally base their assumption on a combination of detailed patient history factors (including occupational and hobby-related exposures), and, where available, ingredient lists or safety data sheets corresponding to the suspected source of dermatitis. Furthermore, patients were included in the group of 'current relevance' if at least one positive reaction to the baseline Spanish series [10] had been classified with current relevance. Other variables, including age, gender, occupational dermatitis (source of exposure in the work area or occupational setting) and occupation, atopic dermatitis, involved site(s) and symptoms duration were collected. All variables were categorised according to the cut-offs indicated in Table S1.

Clinical and demographic variables were presented in function of the current relevance status. All variables were presented as percentages. In order to set the predictive models, the cohort was divided in a training sample (75% of patients) and a validation sample (25% of patients). Area under the curve (AUC) was assigned as the outcome to assess the performance of the models. The AUC ranges from 0.5 (no discriminatory ability, equivalent to random chance) to 1.0 (perfect discrimination), with values above 0.6 generally considered moderate, above 0.7 good, and above 0.9 excellent discrimination [11]. First, a predictive model was established by means of logistic regression. Development of the logistic regression model included goodness-of-fit, discrimination, as well as calibration curves. Univariate logistic regression with the clinical and demographic variables (MOAHLFA index variables, ad-hoc categorised age groups, symptoms duration, main site involved, current specific occupation) and later multivariate logistic regression were performed to obtain the odds ratio (OR) of current relevance. Then, additional machine learning (ML) prediction models, LASSO and gradient boosting, were developed and used to obtain the AUC parameters. Furthermore, for allergens that were associated with current relevance in 400 patients or more, a sub-analysis of the predictive models and associations was also performed.

Missing values for independent variables were excluded from the analyses and models, assuming complete-case analysis under a scenario of missing at random values. Therefore, the modelling dataset was restricted to patients without missing values ($n = 15\,928$). Furthermore, missing data for each MOAHLFA category are reported in Table 1.

All analyses were carried out using STATA v.17.0 (Stata Corp. 2021) and *pystacked* (a Stata API for Phyton scikit-learn's ML algorithms).

The registry was approved by the Complejo Hospitalario Universitario Insular-Materno Infantil Ethics Committee (2017/964) and its operation complies with the Declaration of Helsinki. All patients signed mandatory informed consent to participate. REIDAC collects online data using the REDCap platform.

3 | Results

3.1 | Demographic and Clinical Characteristics

Seventeen thousand and five patients were patch tested during the studied period, with 7727 patients presenting at least 1 positive patch test reaction and 4077 patients presenting at least a current relevant reaction to an allergen of the Spanish baseline series. The demographic features of the cohort can be found in Table 1.

TABLE 1 | Clinical and demographic features of the cohort.

Variable	No current relevance[a]; *n* (%)	At least one current relevance; *n* (%)	Total
Total	12 928 (76.0)	4077 (24.0)	17 005 (100)
Sex; *n* (%)			
Woman	8985 (69.5)	2969 (72.8)	11 954 (70.3)
Men	3939 (30.5)	1108 (27.2)	5047 (29.7)
Missing			4 (0.0)
Occupational dermatitis; *n* (%)			
No	11 475 (92.9)	3228 (82.0)	14 703 (86.5)
Yes	871 (7.1)	707 (18.0)	1578 (9.3)
Missing			724 (4.3)
Atopic dermatitis; *n* (%)			
No	10 262 (80.3)	3337 (83.1)	13 599 (80.0)
Yes	2518 (19.7)	680 (16.9)	3198 (18.8)
Missing			208 (1.2)
Hands; *n* (%)			
No	9100 (70.5)	2523 (62.0)	11 623 (68.4)
Yes	3811 (29.5)	1547 (38.0)	5358 (31.5)
Missing			24 (0.1)
Legs; *n* (%)			
No	12 281 (95.1)	3887 (95.5)	16 168 (95.1)
Yes	630 (4.9)	183 (4.5)	813 (4.8)
Missing			24 (0.1)
Face; *n* (%)			
No	9544 (73.9)	3268 (80.3)	12 812 (75.4)
Yes	3367 (26.1)	802 (19.7)	4169 (24.5)
Missing			24 (0.1)
Age > 40 years; *n* (%)			
No	4222 (32.7)	1338 (32.9)	5560 (32.7)
Yes	8690 (67.3)	2733 (67.1)	11 423 (67.2)
Missing			22 (0.1)
Age; mean (SD)	48.4 (18.6)	47.7 (17.4)	48.2 (18.3)
Age groups; *n* (%)			
0–11 years	221 (1.7)	58 (1.4)	279 (1.6)
12–18 years	477 (3.7)	121 (3.0)	598 (3.5)
19–30 years	1796 (13.9)	540 (13.3)	2336 (13.8)
31–65 years	7767 (60.2)	2673 (65.7)	10 440 (61.5)
≥ 66 years	2651 (20.5)	679 (16.7)	3330 (19.6)
Symptoms duration; *n* (%)			
< 3 months	947 (7.7)	255 (6.6)	1202 (7.4)

(Continues)

TABLE 1 | (Continued)

Variable	No current relevance[a]; *n* (%)	At least one current relevance; *n* (%)	Total
3–12 months	3394 (27.5)	1140 (29.4)	4534 (28.0)
12–36 months	4646 (37.7)	1406 (36.2)	6052 (37.4)
3–5 years	1210 (9.8)	351 (9.0)	1561 (9.6)
> 5 years	2127 (17.3)	727 (18.7)	2854 (17.6)
Main location involved at diagnosis; *n* (%)			
Hand	3811 (29.5)	1547 (38.0)	5358 (31.6)
Head	564 (4.4)	274 (6.7)	838 (4.9)
Face	3367 (26.1)	802 (19.7)	4169 (24.6)
Oral	312 (2.4)	79 (1.9)	391 (2.3)
Neck	364 (2.8)	143 (3.5)	507 (3.0)
Trunk	2108 (16.3)	551 (13.5)	2659 (15.7)
Anogenital	386 (3.0)	89 (2.2)	475 (2.8)
Arm/Forearm	796 (6.2)	184 (4.5)	980 (5.8)
Thigh/Knee	260 (2.0)	61 (1.5)	321 (1.9)
Leg	630 (4.9)	183 (4.5)	813 (4.8)
Foot	313 (2.4)	157 (3.9)	470 (2.8)
Main occupation; *n* (%)			
Senior technician	321 (2.5)	87 (2.1)	408 (2.4)
Health worker	1018 (7.9)	341 (8.4)	1359 (8.0)
Teacher	405 (3.1)	124 (3.0)	529 (3.1)
Mid-level technician	232 (1.8)	55 (1.3)	287 (1.7)
Administrative	1507 (11.7)	458 (11.2)	1965 (11.6)
Service sector	679 (5.3)	208 (5.1)	887 (5.2)
Waiter	276 (2.1)	105 (2.6)	381 (2.2)
Hairdresser/Beautician	303 (2.3)	245 (6.0)	548 (3.2)
Sales	370 (2.9)	118 (2.9)	488 (2.9)
Construction supervisor	119 (0.9)	65 (1.6)	184 (1.1)
Mechanic	160 (1.2)	65 (1.6)	225 (1.3)
Food processing	271 (2.1)	95 (2.3)	366 (2.2)
Driver	96 (0.7)	24 (0.6)	120 (0.7)
Cleaner	485 (3.8)	164 (4.0)	649 (3.8)
Housekeeper	157 (1.2)	48 (1.2)	205 (1.2)
Construction labourer	78 (0.6)	38 (0.9)	116 (0.7)
Homemaker	1104 (8.5)	326 (8.0)	1430 (8.4)
Student	1348 (10.4)	351 (8.6)	1699 (10.0)
Retiree	2324 (18.0)	580 (14.2)	2904 (17.1)
Unemployed	390 (3.0)	109 (2.7)	499 (2.9)
Others	1285 (9.9)	471 (11.6)	1756 (10.3)

[a]Note that 'no current relevance' includes patch test negative patients and those with at least one positive test but unknown relevance. SD (standard deviation).

3.2 | Predictive Models and Association With Allergic Contact Dermatitis

Predictive models were based on data from 15928 patients (93.7% of the sample), who were divided in a training ($n = 12002$; approximately 75%) and validation sample ($n = 3926$; approximately 25%). The AUC parameters of the logistic regression were obtained for both the training (AUC: 0.683; LL 95% CI: 0.671—UL 95% CI: 0.694) and validation samples (0.679; 0.659–0.698). Curve calibration slope was 0.987 with an AUC of 0.679 (Figure S1). The AUC parameters for the validation sample were also obtained with two other ML predictive methods (LASSO and gradient boosting). Performance with the three approaches was similar, with gradient boosting obtaining the best performance by a small margin (0.683; 0.663–0.702). Table 2 shows the data of all the predictive models studied.

In regard to the association of clinical parameters and likelihood of clinical variables, some categories of sex, location and occupation were increasingly or decreasingly associated with the dependent variable. Being a woman, site (hand, neck, head, leg, feet) versus face, and two occupations (hairdressers and construction workers vs. other occupations) were associated with an increased risk of presenting a current relevant reaction. In contrast, among all the clinical variables, only some occupations were associated with a decreased likelihood of presenting a current reaction, including health workers, sales workers, students, homemakers and retirees (vs. other occupations).

Figure 1 shows the dot plot of the odds ratio for the clinical variables and the visual performance of the prediction models of the validation sample.

TABLE 2 | Performance of prediction models for overall current relevance in the validation sample.

Model	Total	AUC	LL 95% CI	UL 95% CI
Logistic	3926	0.679	0.659	0.698
LASSO	3926	0.679	0.660	0.698
Gradient boosting	3926	0.683	0.663	0.702

Abbreviations: AUC, area under the curve; LL 95% CI, lower limit 95% confidence interval; UL 95% CI, upper limit 95% confidence interval.

3.3 | Predictive Models and Association With Frequent Allergens

In this study, only four haptens (or hapten mixes) matched with the methodological criteria to be further sub-analysed, including nickel, methylisothiazolinone, methylchloroisothiazolinone/methylisothiazolinone, and fragrance mix I. The detailed percentages of current relevance for all allergens can be found in Table S2.

The prediction models for the most frequent allergens have shown the best performances for nickel sulfate (Gradient boosting; 0.773; 0.740–0.807) and methylchloroisothiazolinone/methylisothiazolinone (LASSO; 0.728; 0.680–0.776). For the fragrance mix I and methylisothiazolinone, prediction models underperformed the overall performance for all allergens. In this sub-analysis, logistic regression and gradient boosting performed similarly within each hapten. Furthermore, among both isothiazolinones, LASSO modelling had a better performance than all

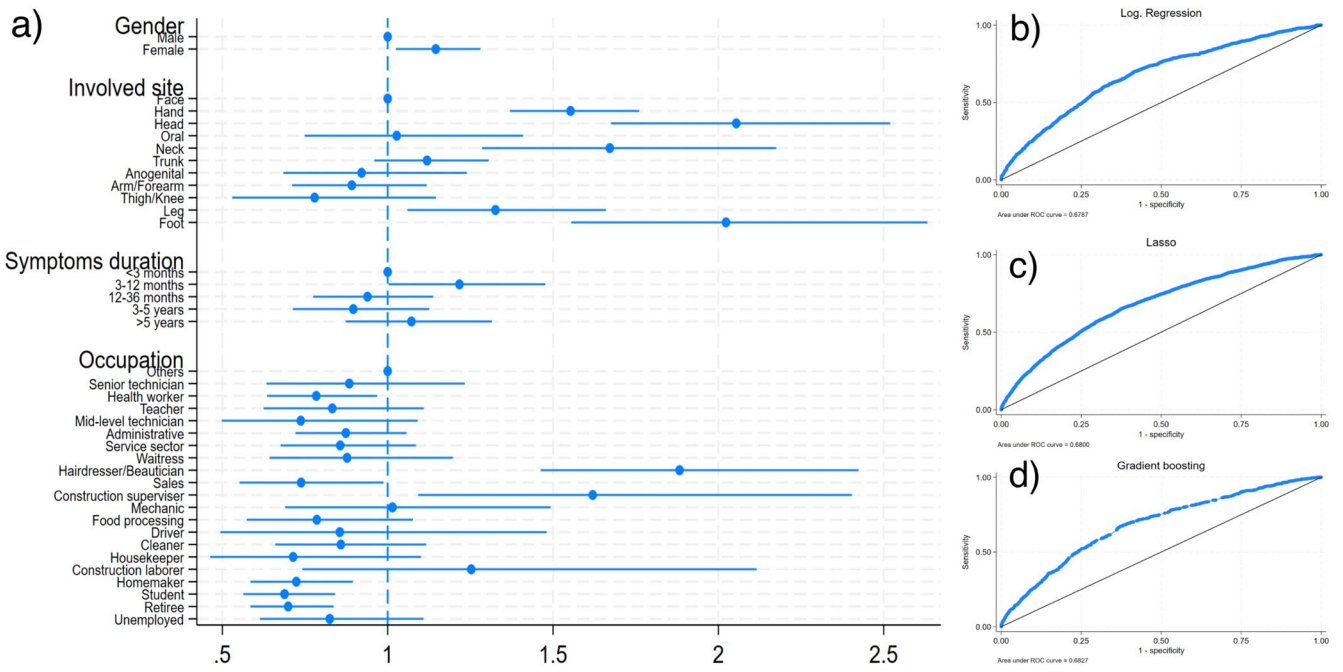

FIGURE 1 | Factors associated with overall current relevance and graphical performance of different predictive models for overall current relevance. (a) Odds ratio dot plot showing the clinical-demographic factors and their association to overall current relevance using multivariate logistic regression; (b) Graphical performance of the predictive model with logistic regression; (c) Graphical performance of the predictive model with the LASSO method; (d) Graphical performance of the predictive model with the gradient boosting method.

TABLE 3 | Performance of prediction models for selected allergens in the validation sample.

Model	Total	AUC	LL 95% CI	UL 95% CI
Nickel				
Logistic	3907	0.770	0.736	0.804
LASSO	3916	0.769	0.734	0.803
Gradient boosting	3916	0.773	0.740	0.807
Methylisothiazolinone				
Logistic	3439	0.650	0.609	0.691
LASSO	3521	0.661	0.621	0.700
Gradient boosting	3521	0.653	0.613	0.692
Methylchloroisothiazolinone/Methylisothiazolinone				
Logistic	3047	0.697	0.647	0.747
LASSO	3269	0.725	0.678	0.772
Gradient boosting	3269	0.728	0.680	0.776
Fragrance mix I				
Logistic	3904	0.622	0.564	0.681
LASSO	3916	0.651	0.593	0.709
Gradient boosting	3916	0.627	0.567	0.688

Abbreviations: AUC, area under the curve; LL 95% CI, lower limit 95% confidence interval; UL 95% CI, upper limit 95% confidence interval.

other models. Table 3 shows the exact values for all the models and allergens.

Regarding the association of clinical variables and current relevance, the findings were different for each allergen. Nickel was the allergen that revealed a higher number of associations. For this hapten, being a woman, a middle-aged adult (vs. older adults), oral mucosa, trunk, head and hand (vs. face) involvement, as well as symptoms duration higher than 5 years (vs. 3 months) were associated with an increased risk of presenting a positive reaction with current relevance. Furthermore, anogenital involvement (vs. face), as well as some occupations (health worker, teacher and technician) were associated with a lower risk. Concerning isothiazolinones, methylchloroisothiazolinone/methylisothiazolinone analysis only showed that hand involvement was associated with an increased risk of current relevance whereas methylisothiazolinone analysis revealed more associations. In this line, older age frames, hand involvement (vs. face) and both subacute (3–12 months) and long-standing (> 5 years) symptoms duration were associated with an increased likelihood, while being a woman and feet involvement were linked to a decreased likelihood of current relevance. Regarding fragrance mix I, only neck (vs. face) involvement had an increased likelihood of current relevance, whereas being an adolescent or young adult and head dermatitis (vs. face) had a lower probability of finding a current relevant result. Figure 2 shows the dot plots for the four allergens.

4 | Discussion

In this study, both overall and allergen-specific current relevance have only been moderately predicted by different models. However, daily-practice clinical variables seem to contribute to the prediction modelling of current relevance. This finding is reinforced by the associations revealed by the logistic regression analyses, showing that several variables are associated with current relevance.

In terms of prediction capacity of models, overall prediction of current relevance was poorer than for frequently encountered allergens. Within the dissection of different models for overall prediction, gradient boosting had the better performance, in accordance with previous studies [7]. It has been hypothesised that this may be due to gradient boosting being able to capture nonlinear relationships between variables [7]. The prediction modelling for allergens showed better performance of the models for nickel sulfate and methylchloroisothiazolinone/methylisothiazolinone, but this could not be seen for all other studied allergens. In fact, the prediction performance was allergen-dependent. Rationale for allergen-dependent differences may lie on different features including higher probability of sensitization to a given hapten (e.g., widespread allergen or with high sensitising properties) [12–14], genetic individual-related factors [15], as well as some haptens being associated with particular clinical or demographic features (e.g., nickel and piercing practices [16]).

The study of the association of clinical/demographic parameters with the overall occurrence of current relevant results as well as the specific allergen sub-analysis has revealed multiple associations. In terms of associations with current relevance in the overall model, some body locations and occupations showed the highest odds ratio. In this study, the addition to the model of 'anatomical sites involved' has revealed new associations of current relevance that may not have been proven in previous studies. In this regard, involvement of foot, head, neck, hands and legs has been previously associated with a higher frequency of positive patch test reactions and/or polysensitization [17–19]. Several well-known and traceable factors could explain this association with current relevance, including the frequent application of topical products (e.g., face, feet or legs) [20], the high interaction with allergens (e.g., hands) [21], and/or sociodemographic habits (e.g., application of fragrances in the neck and upper chest region) [22]. With regard to occupations, being a hairdresser-beautician or a construction worker has been consistently associated with finding a current relevance. Both occupations are linked to a high burden of ACD, and many of the causative allergens are well-known among workers and dermatologists, as well as found in complementary patch test series [23–25]. Previous works have also shown that current relevant positive results may be frequently found in these occupational groups [26, 27]. This may ease the description of current relevance in comparison to other occupations, for which lesser-known allergens may not be studied and/or relevance incorrectly assessed [28, 29]. Finally, being a woman was associated with an increased likelihood of finding a current relevance. We hypothesise that this may be due to different patterns of domestic and personal care exposure to haptens.

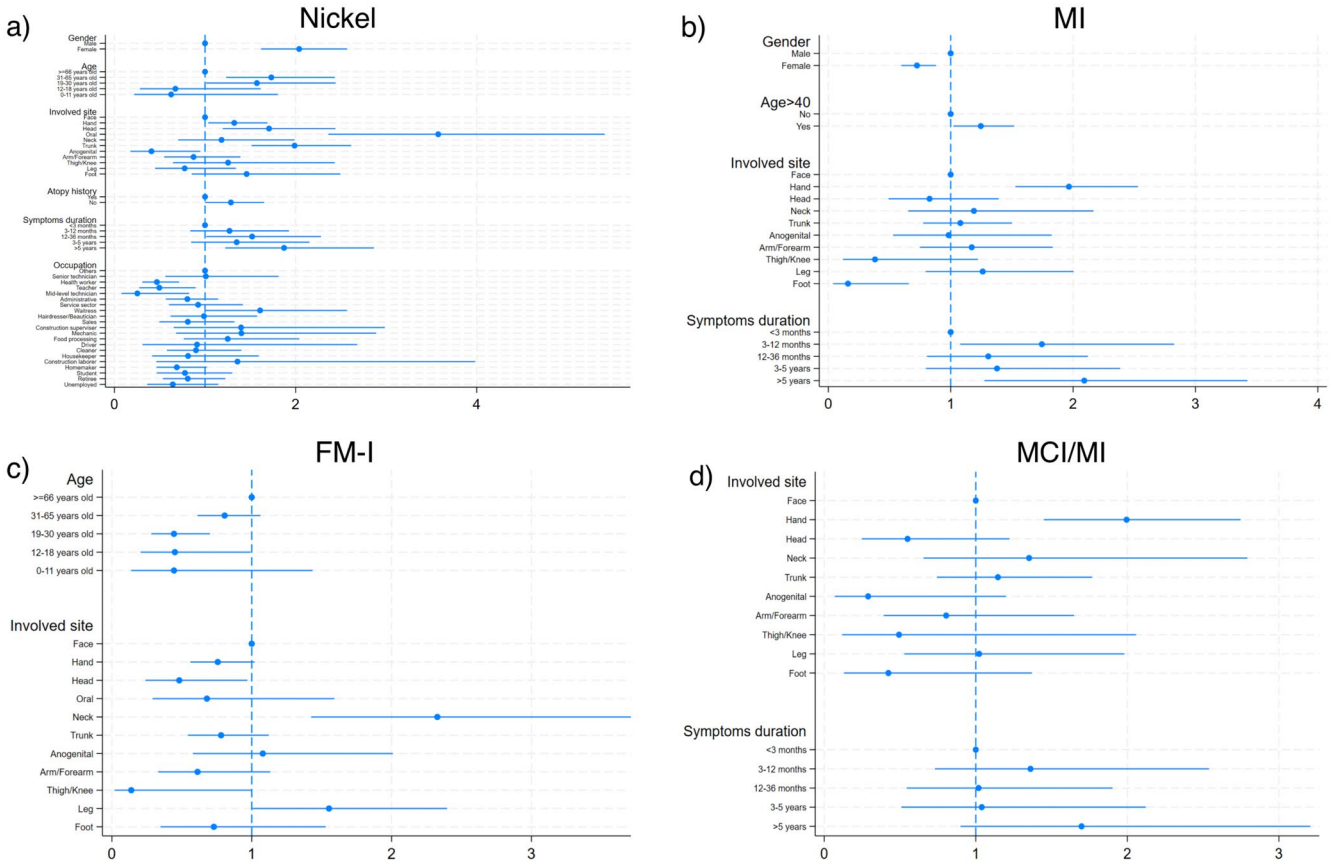

FIGURE 2 | Factors associated with current relevance across the most frequently relevant allergens. (a) Sub-analysis of nickel; (b) Sub-analysis of methylisothiazolinone (MI, in the figure); (c) Sub-analysis of fragrance mix I (FM-I, in the figure); (d) Sub-analysis of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI, in the figure).

The study of association of clinical/demographic parameters with the individual hapten results for current relevance has revealed sex as well as some age groups, body involvement and disease duration as clinically related to the finding of clinical relevance. It is important to note that some aspects associated with current relevance that take place in clinical practice are being captured by the predictive models, and confirming their importance and potential traceability in larger groups of patients. Thus, some locations occur to be associated with current clinical relevance, possibly in relation to frequent sites of exposure and well-known clinical patterns by the clinicians, such as trunk and nickel ('belly' dermatitis) [30], hand and both isothiazolinones (hand eczema and isothiazolinones) [31, 32] or neck dermatitis and fragrance mix I [22]. In relation to sex, the association of being a woman with current relevance in nickel may reflect sociodemographic patterns involving women more frequently such as earring/piercing practices and use of jewellery [16]. With regard to the long duration (> 5 years) of the dermatitis associated with current relevance in nickel, it is believed that this is linked to the previous fact. This predictive study of associations may reveal other associations that are not well known or characterised, generating future hypotheses (e.g., oral mucosa and current relevance in the nickel sub-analysis).

Some of the allergens (e.g., nickel sulphate, methylisothiazolinone and methylchloroisothiazolinone) with highest relevance in this study are regulated in the European Union due to which these results may need further analyses. Recent studies have proved that there has been a significant decrease in the frequency and/or relevance of nickel, methylisothiazolinone and methylchloroisothiazolinone contact allergy [5, 33–35]. However, these allergens continue to present with significant relevance in current studies (in Europe [4], and elsewhere [36]). Reasons for this could be that current regulations apply only to some products (e.g., methylisothiazolinone still widely present in cleaning or industrial products [37]), use of less regulated products (e.g., imported products [37]), individual susceptibility which may lead to sensitization despite low-level exposures and long-term occupational exposures (e.g., nickel-releasing metals [38]), among others. Furthermore, this decrease has been uneven in different regions of Europe, with still higher percentages in Southern Europe [30]. Further reasons for this could be incomplete labelling and even potential variability in enforcement [39].

Overall, the data resulting from prediction models, either global or allergen-specific, indicate that the occurrence of current relevance may be explained, at least partially, by the set of independent variables in our study. However, the diagnostic accuracy of these models, at this current moment, cannot replace the evaluation performed by a trained clinician. This can be explained by the difficulty in dissecting the many potential variables that contribute to the occurrence of ACD as well as to explain why an agent is leading to ACD in a certain manner.

This study has strengths as well as several limitations that need to be discussed. The strengths of the study lie in the high number of patients included, with the possibility of creating both training and validation samples, as well as the similar results obtained between both samples, and the real life setting of the study, which may capture better variability in predictive studies. Furthermore, this study has added the site involvement to the prediction model and has evidenced its relevance in this setting. There are some limitations to mention, including that the evaluation of clinical relevance may not capture the correct relationship between the allergen and patients' reactions, leading to unintentional misclassification of clinical relevance. This may particularly occur with less frequent allergens or undeclared allergens. Furthermore, in the setting of a multi-centric study, patch testing has been performed in different Contact Dermatitis units, with different allergen preparations, which may result in a certain degree of heterogeneity in the interpretation of patch test reactions and their relevance.

In conclusion, prediction modelling for current relevance may moderately predict it in clinical practice. Despite this approach complementing the knowledge of the clinician, it does not substitute it in daily practice. However, predictive models may complement the evaluation of patients and be useful in the design of clinical guidelines or algorithms [40]. Our study highlights clinical relationships between ACD/allergens and clinical relevance that are known in clinical practice, as well as bringing new associations (e.g., specific body involvement areas for specific allergens) that will require further studies.

Author Contributions

Francisco Navarro-Triviño: validation, writing – review and editing, data curation. **Gemma Melé-Ninot:** validation, writing – review and editing, data curation. **Fátima Tous-Romero:** validation, writing – review and editing, data curation. **David Pesqué:** conceptualization and writing original draft preparation. **Miguel Ángel Descalzo and Ignacio García-Doval:** data curation, methodology, formal analysis, validation, review and editing. **David Pesqué, Francisco Javier Ortiz de Frutos, Francisco Navarro-Triviño, Tatiana Sanz-Sánchez, Violeta Zaragoza-Ninet, Susana Córdoba-Guijarro, Javier Miquel-Miquel, Juan Francisco Silvestre-Salvador, Ricardo González-Pérez, Inmaculada Ruiz-González, Pedro Mercader-García, Esther Serra-Baldrich, José Manuel Carrascosa-Carrillo, Fátima Tous-Romero, Mercedes Rodríguez-Serna, María Elena Gatica-Ortega, Carmen Paredes-Suárez, María Antonia Pastor-Nieto, Pablo Chicharro, Marta Andreu, Araceli Sánchez-Gilo, José Juan Pereyra-Rodríguez, Gemma Melé-Ninot, Paloma Sánchez-Pedreño Guillén, Enrique Gómez de la Fuente, Marta Elosua-González, Fernando Gallardo, Ramon M. Pujol, Ignacio García-Doval, Leopoldo Borrego, Miguel Ángel Descalzo, Ana M. Giménez-Arnau:** data curation, validation, review and editing.

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Conflicts of Interest

D.P. has received research funding from LEO Foundation and has received funding for congress attendance or been a speaker for Novartis, Almirall, and LeoPharma outside the submitted work. J.M.-M. received fees as speaker from Lilly, Leo-Pharma, Novartis, Abbvie, Amgen, Pfizer and Janssen, has been Principal Investigator in clinical trials sponsored by Amgen, Novartis, Abbvie, and Almirall, and has participated in Advisory Boards organised by Sanofi, Novartis, Leo-Pharma, Pfizer, Almirall, and Abbvie outside the submitted work. P.M.-G. reports lectures and advisory boards from Sanofi, Leo Pharma, Lilly, Almirall, and AbbVie outside of the scope of the submitted work. G.M.-N. has been Medical Advisor for

Abbvie, Leo Pharma, Lilly, Sanofi, and Novartis and has participated in educational activities for Almirall, Avène, Abbvie, Laboratorio Reig Jofre, Leo Pharma, Lilly, Meda, Novartis, Sanofi, and Uriage outside the submitted work. I.G.-D. has received funding for congress attendance from Abbvie, MSD, Pfizer and Sanofi outside the submitted work. A.M.G.-A. is or recently was a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Celldex, Escient Pharmaceuticals, Genentech, GSK, Instituto Carlos IIIFEDER, Leo Pharma, Menarini, Mitsubishi Tanabe Pharma, Novartis, Sanofi-Regeneron, Servier, Thermo Fisher Scientific, Uriach Pharma, Noucor outside the submitted work.

Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Curve calibration of the validation sample AUC (area under the curve), CI (confidence interval), CITL (calibration in the large), E:O (expected: observed). **Table S1:** Specification on the categorisation of study variables. **Table S2:** Percentage of current relevance for all allergens.