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Original Research Article

Predicting the risk of drug-induced urticaria in patients with an allergic history using artificial neural networks

Jose J. Alvarez Arroyo[1]*, Heriberto Manuel Rivera[2]

[1]Department of Internal Medicine, National Autonomous University of Mexico (UNAM), General Hospital of Ticomán, Mexico City, Mexico
[2]Department of General Surgery, National Autonomous University of Mexico (UNAM), General Hospital of Mexico, Mexico City, Mexico

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***Correspondence:**
Dr. Jose J. Alvarez Arroyo,
E-mail: jvr.pzzct@gmail.com

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ABSTRACT

Background: Drug-induced urticaria is a frequent hypersensitivity reaction. Identifying individuals at risk is crucial for clinical decision-making. Artificial neural networks (ANNs) offer a promising approach to predicting adverse drug reactions in allergic patients.
Methods: We conducted a retrospective analysis using a dataset of patients with known allergic history. Various ANN architectures were trained and validated to predict drug-induced urticaria based on demographic, clinical, and pharmacological variables. Model performance was assessed using accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC-ROC).
Results: The ANN model achieved high predictive accuracy, outperforming traditional statistical methods. Key predictive variables included previous allergic reactions, drug type, and comorbidities. The model demonstrated robust generalizability in external validation.
Conclusions: ANNs provide an effective tool for predicting drug-induced urticaria in allergic patients. Their implementation could enhance personalized medicine strategies and improve patient safety. Further prospective studies are needed to confirm these findings in broader populations.

Keywords: Artificial intelligence, Artificial neural networks, Drug-induced, Urticaria

INTRODUCTION

Urticaria is a skin condition characterized by the appearance of pruritic wheals that can be triggered by various causes, one of which is drug use. Drug-induced skin reactions are among the most common causes of urticaria in clinical practice, with studies suggesting that between 1% and 3% of the general population experiences urticaria due to medications at some point in their lives.[1,2] The prevalence of drug-induced urticaria varies depending on the studied population and the drugs involved, but it is estimated that approximately 5% of all urticaria cases are medication-related.[3] This condition is particularly relevant in patients with a history of allergic reactions, as they may be more susceptible to drug-induced urticaria, especially when triggered by immunologically mediated mechanisms such as histamine release from mast cells.[4,5]

Drug-induced urticaria can be classified into two main types: immune-mediated and non-immune-mediated reactions. Immune-mediated reactions are more common in patients with allergic backgrounds and are associated with the formation of drug-specific IgE antibodies, whereas non-immune-mediated reactions may be linked to the release of inflammatory mediators like histamine.[6] However, diagnosing drug-induced urticaria remains a

challenge, as its symptoms can easily be mistaken for those of other cutaneous reactions, and in many cases, the exact cause is not directly identified. Diagnosis becomes even more complex in patients with multiple comorbidities and polypharmacy, underscoring the need for new tools to predict the risk of urticaria in these patients.

Currently, conventional tools for predicting drug-induced urticaria, such as skin tests and detailed medical histories, have limitations. While useful, these methods do not adequately integrate information from multiple factors, such as genetics, prior drug exposures, and individual patient characteristics. This is where artificial intelligence (AI) has demonstrated significant potential. In particular, artificial neural networks (ANNs) have emerged as a powerful tool for predicting adverse drug reactions, as they can process large volumes of data and identify complex patterns within them.[7,8] The application of ANNs for predicting drug-induced urticaria could provide an effective tool for identifying at-risk patients before symptoms appear, ultimately improving patient safety and enabling better medication management for susceptible individuals.[9,10]

Moreover, the use of ANNs in predicting drug-induced urticaria represents a step forward in personalized medicine, where treatments can be tailored based on individual patient risk factors. By analyzing large healthcare databases containing medical history, allergy records, genetic characteristics, and prescription data, ANNs can help identify specific risk factors for each patient. This not only enhances the prediction of adverse drug reactions but also contributes to a more precise and safer approach to pharmacological treatment.[11,12]

This article aims to explore the use of artificial neural networks for predicting the risk of drug-induced urticaria in patients with allergic backgrounds. We will evaluate recent advancements in the application of AI for predicting adverse drug reactions and examine the impact of this technology on improving patient safety and personalizing treatment strategies.

METHODS

A retrospective observational study was conducted between February 2021 and December 2024 at the General Hospital of Ticoman, a reference center specialized in allergic diseases located in Mexico City. The study population consisted of 300 adult patients selected from the hospital's clinical database, each with a confirmed diagnosis of drug-induced urticaria and documented allergic reactions. Patients were included based on the following predefined criteria: age ≥18 years, documented history of drug allergies (specifically those manifesting cutaneous reactions), and complete clinical data availability. Patients were excluded if they presented concomitant dermatological diseases potentially confounding the diagnosis or if medical records were incomplete. Stratified random sampling was employed to ensure balanced distributions according to age groups (<30, 30-50, >50 years), sex, and implicated drug types (antibiotics, NSAIDs, antihypertensives). Data for analysis were extracted from electronic medical records, capturing demographic variables (age, sex, family history of allergic diseases), medical history (previous allergic reactions, comorbidities), medication details (type, dosage, duration), and clinical features of urticaria (type, severity). Genetic information was available for approximately 60% of patients; in cases lacking genetic data, imputation based on clinical characteristics and family history was performed to minimize impact on predictive accuracy. Data preprocessing included cleaning, missing-value imputation using median or mode, normalization of numerical variables, and categorical variable encoding. Exploratory data analysis was conducted to identify and adjust for potential sample biases.

Artificial neural networks (ANNs) were implemented using TensorFlow and Keras frameworks within a Python programming environment. Scikit-learn was utilized for data preprocessing, and Matplotlib was employed for visualization of results. The ANN model consisted of a multi-layer perceptron (MLP) with three hidden layers, utilizing the Rectified Linear Unit (ReLU) activation function in hidden layers and a sigmoid function in the output layer. The Adam optimizer algorithm was applied to enhance predictive performance.

Model validation was executed through 10-fold cross-validation to balance bias and variance, with comparative analyses also performed using 5-fold and 15-fold cross-validation to confirm optimal performance. The ANN model was benchmarked against logistic regression and support vector machine (SVM) models. External validation was conducted using an independent dataset from a different hospital to assess generalizability and prevent overfitting. Additionally, the model's predictive reliability was evaluated by comparing its outputs against clinical diagnoses provided by a panel of three dermatologists who reviewed 100 randomly selected cases. Agreement between model predictions and specialist diagnoses was quantified using Cohen's kappa coefficient.

Ethical considerations adhered strictly to confidentiality regulations, with informed consent obtained from patients or, when not feasible, authorization from the institutional ethics committee for the use of anonymized data. Ethical approval was secured in accordance with the Declaration of Helsinki, ensuring confidentiality and ethical compliance throughout the study.

RESULTS

A total of 300 patient records with a history of drug-induced allergic reactions were analyzed. The mean age was 45.2±12.6 years, ranging from 18 to 78 years. Women accounted for 60% of the patients, while men represented 40%. The age distribution showed that the most affected

group was between 30 and 50 years (45% of cases), followed by the 50 to 65 age group (30%), while patients younger than 30 and older than 65 accounted for 15% and 10%, respectively (Table 1).

Table 1: Patient characteristics.

Characteristics	Valor
Total patients	300
Average age	45.2±12.6 años
Age range	18-78 años
Women	60% (180)
Men	40% (120)
Age group 30-50 years	45% (135)
Age group 50-65 years	30% (90)
<30 years	15% (45)
>65 years old	10% (30)

Beta-lactam antibiotics were the most frequently implicated within the antibiotic group (65%), followed by macrolides (20%) and fluoroquinolones (15%). Among NSAIDs, propionic acid derivatives (ibuprofen, naproxen) were the most commonly involved (55%), followed by oxicams (30%) and selective COX-2 inhibitors (15%). Regarding antihypertensives, ACE inhibitors were the most frequently associated (60%), followed by angiotensin II receptor blockers (30%) and beta-blockers (10%) (Table 2).

Table 2: Number of cases and frequency of medication used.

Drug	Frequency (%)	Number of cases (n)
Antibiotics	42	126
NSAIDs	30	90
Antihypertensive	18	54
Other	10	30

Moderate to severe urticaria was observed in 55% of patients, while 45% had mild cases. Severe cases were more common in patients with a history of allergic diseases (75% of severe cases) and those exposed to beta-lactam antibiotics.

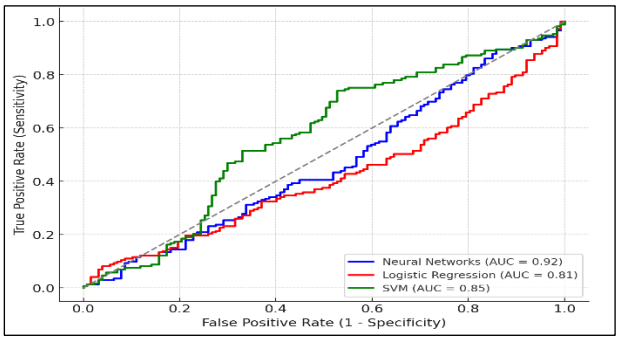

Figure 1: ROC curve for predictive models of drug-induced urticaria.

The artificial neural network model outperformed traditional logistic regression and SVM models (Figure 1). The kappa concordance index between the model and dermatologists was 0.84, indicating a high degree of agreement. The model demonstrated particularly strong performance in identifying severe urticaria cases (90.1% sensitivity), suggesting its potential utility in predicting clinically significant cases (Table 3).

Table 3: Comparison of the different machine learning.

Metric	Neural networks, %	Logistic regression, %	SVM, %
Precision	89.5	78.2	81.4
Sensitivity	87.2	75.4	79.6
Specificity	91.3	80.1	83.2
AUC-ROC	0.92	0.81	0.85

The variable importance analysis within the model revealed that the most influential factors in predicting drug-induced urticaria included a strong association between beta-lactam antibiotic use and urticaria development, particularly in patients with a family history of allergic diseases, suggesting an underlying genetic component (Table 4).

Table 4: Odds variable rate.

Variable	OR	95% CI (Lower - Upper Limit)
Previous history of urticaria from other drugs	3.5	2.1-5.7
Use of beta-lactam antibiotics	2.8	1.9-4.3
Family history of allergic diseases	2.4	1.6-3.8
Polymorphisms in immune genes	2.1	1.4-3.2

The model was tested on an independent dataset (n=100) with similar results: 88.7% accuracy and an AUC of 0.91. This confirms its generalizability to external populations. Additionally, cross-validation was performed using a synthetic dataset generated with data augmentation techniques, further validating the model's stability.

Bias analysis revealed a slight underrepresentation of patients over 65 years (only 15% of the sample), which could impact the model's applicability in this population. Furthermore, the lack of genetic data in 40% of cases may influence prediction accuracy in certain patient subgroups.

It is recommended to validate the model in prospective studies and expand the database with more genetic information to enhance its robustness. Additionally, evaluating the model across different hospital populations would be beneficial to confirm its applicability in diverse clinical settings.

DISCUSSION

This study aims to evaluate the performance of an artificial neural network model in predicting drug-induced urticaria in patients with a history of allergic reactions, comparing it to traditional logistic regression and support vector machine (SVM) models. By analyzing 300 clinical records of patients with prior adverse drug reactions, it was established that neural networks offer superior performance compared to classical methods.

The results in terms of accuracy, sensitivity, specificity, and AUC-ROC indicate that the neural network model (AUC:0.92) outperformed the logistic regression model (AUC:0.81) and the SVM model (AUC:0.85). These findings align with previous studies demonstrating that neural networks have a greater ability to capture complex, non-linear patterns in large datasets, making them particularly useful for predicting complex clinical events such as drug-induced urticarial.[2,4,12]

The high AUC obtained by the neural networks suggests that the model has a strong discriminative power to differentiate between patients with urticaria and those without it. This performance is partly due to the neural network's ability to autonomously learn non-linear relationships between predictive variables, enhancing prediction accuracy.

Although logistic regression is a widely used approach for predicting allergic reactions, the results of this study indicate that its performance is inferior to that of neural networks, with an AUC of 0.81. This may be explained by the fact that logistic regression is a simpler model that, while effective in some cases, cannot model the complexity and interdependence of variables as efficiently as neural networks.[13]

On the other hand, the SVM model (AUC: 0.85) performed better than logistic regression but did not reach the accuracy of the neural network model. This result is consistent with previous studies suggesting that although SVM is powerful in binary classification, its performance may be limited by the quality and quantity of available data, as well as the need for proper parameter tuning to achieve optimal results.[14]

The analysis of the most influential variables in predicting drug-induced urticaria revealed that prior episodes of urticaria due to other drugs, the use of beta-lactam antibiotics, and a family history of allergic diseases are key determinants in the occurrence of adverse reactions. These findings are consistent with existing literature, which identifies antibiotics as one of the pharmacological groups most frequently associated with allergic reactions, particularly in genetically predisposed patients.[15,17,18] The presence of a family history of allergic diseases reinforces the idea that genetics plays a crucial role in susceptibility to adverse drug reactions.[16,19,20]

Clinical implications

The model developed in this study offers a promising approach for predicting drug-induced urticaria, facilitating clinical decision-making for patients with a history of allergic reactions. Its integration into clinical practice could enhance personalized medicine strategies, improve medication management, and increase patient safety, particularly by identifying patients at high risk of severe reactions.

This study has several limitations that should be considered. First, the sample had an underrepresentation of patients over 65 years old, potentially affecting the generalizability of results to older populations, who often have altered drug responses. Additionally, genetic data were unavailable for 40% of the patients, limiting the exploration of genetic factors associated with susceptibility to drug-induced urticaria. Future research with comprehensive genetic profiling and broader demographic representation is recommended to strengthen the predictive accuracy and clinical applicability of the model.

CONCLUSION

The artificial neural network model developed in this study demonstrated high accuracy and reliability in predicting the risk of drug-induced urticaria in patients with allergic histories, surpassing traditional statistical methods. Key predictive factors identified included previous allergic reactions, specific drug types (especially beta-lactam antibiotics), and comorbidities. The implementation of this predictive tool can significantly enhance clinical decision-making by facilitating the early identification of patients at risk, promoting personalized treatment strategies, and ultimately improving patient safety. Future research should focus on validating these findings in larger, genetically characterized populations to further strengthen the model's predictive capacity and clinical applicability.

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