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ARTIFICIAL INTELLIGENCE FOR PATIENT SAFETY IN PHARMACOVIGILANCE

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ABSTRACT

AI (XAI) is a methodology that complements the black box of artificial intelligence, and its necessity has recently been highlighted in various fields. The purpose of this research is to identify studies in the field of pharmacovigilance using XAI. AI can improve the efficiency and accuracy of signal detection, enabling pharmacovigilance teams to prioritize and investigate according to patient illness like diabetic retinopathy and chronic disease and take most important safety concerns. As technology continues to advance, it is important for healthcare providers and researchers to continue exploring the potential benefits and limitations of AI in pharmacovigilance in order to maximize its impact on patient safety. Finally, key challenges for several research issues for the use of XAI in pharmacovigilance were identified. Although artificial intelligence (AI) is actively used in drug surveillance and patient safety, gathering adverse drug reaction information, extracting drug-drug interactions, and predicting effects, XAI is not normally utilized.

Keywords: Artificial Intelligence, Drugs, Predictive Models, Data Models, Safety, Machine Learning, Databases.

I. INTRODUCTION

The World Health Organization defines pharmacovigilance (PV) as the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems [1].

Recent artificial intelligence-based technologies can be an efficient complement to traditional PV methods, which can be costly and time-consuming and can result in adverse drug reactions(ADRs) professionals.

Artificial intelligence (AI) can improve PV, but its use in PV is still in the early stages of research. Various machine learning (ML) techniques, together with natural language processing and data mining, can be applied to electronic health records, claims databases and social media data to improve the characterization of known drug side effects and reactions, and to detect new signals [2], [3].

AI-based technologies have been criticized for their inexplicable algorithms, despite their high predictive power. In critical decision areas such as healthcare, the reasoning behind a decision is as important as the decision itself, which is why there is growing interest in and research and development around Explainable Artificial Intelligence (XAI).

XAI was developed to improve the transparency of AI systems and generate explanations for them, and seeks to increase trust and understanding by assessing the strengths and limitations of existing models [4], [5], [6]. Approaches that extract information from a model's decision-making process, such as post-hoc explanations, can provide useful information for practitioners and users interested in case by-case explanations rather than the internal workings of a model [7].

XAI increases the explainability and transparency of AI algorithms by making it possible to interpret the variables that influence decisions, complex internal features, and learned decision paths within a decision process [8], [9]. I.R. Ward et al. successfully quantified the importance of features using an XAI algorithm, further demonstrating the potential contribution of XAI to PV monitoring [10].

The importance of PV in medicine is relevant to all species affected by medical interventions, and ensuring medical safety requires attention and research into approaches such as drug safety reporting and the exchange of reliable and timely information on PV activities [11]. The global pharma covigilance and drug safety software market size was valued at USD 6.9 billion in 2021 and is estimated to expand at a compound growthrate(CAGR)of10.5% between 2022 and 2030.

The aim of this study was to review the literature on the use of XAI in PV by identifying publications related to ML/AI and drugs and the rationale for the reported findings. From the perspective of AI and XAI usage, these studies were analyzed, and the findings were summarized, in which the use of XAI in the field of PV is referred to as ''PV XAI''. The main contributions are highlighted and discussed below:

This study is clearly an early attempt to review XAI research in PV. Unlike other fields, we found that XAI research in PV is at an early stage of development, limited to a few articles and some methodologies.

Nevertheless, we have identified the positive potential of PVX AI for drug therapy, ADRs, polypharmacy and drug repurposing.

While safety issues in real-world healthcare settings may limit the growth of the field, we expect PV XAI research to expand as it has in other areas, and we encourage collaboration and ongoing research discus sions with experts in the field.

II. LITERATURE REVIEW

1. **J.K. Aronson, ''Artificial intelligence in pharmacovigilance: An introduction to terms, concepts, applications, and limitations,'' Drug Saf., vol. 45, no. 5, pp. 407–418, May 2022, doi: 10.1007/s40264-022- 01156-5.**

In this study, the trend of XAI in the field of PV was examined. However, the trend was also explored broadly to more diverse aspects, including interpretable artificial intelligence. Although there is a clear difference between Explainable AI (knowledge about what different nodes represent and their importance to model performance) and Interpretable AI (ability to determine cause and effect in a machine learning model), based on the same aim, they were comprehensively reviewed.

2. **Y I. R. Ward, L. Wang, J. Lu, M. Bennamoun, G. Dwivedi, and F. M. Sanfilippo, ''Explainable artificial intelligence for pharmacovigilance: What features are important when predicting adverse outcomes?'' Comput. Methods Programs Biomed., vol. 212, Nov.2021, Art. no. 106415, doi: 10. 1016/j. cmpb. 2021. 106415.:**

The selection of appropriate search terms for the explo ration of XAI-related research in PV was not easy; we started manually with broad keywords. The following five searches were performed: pharmacovigilance XAI (47), pharmacovigilance ''explainable artificial intelligence'' (76), pharmacovigilance explainable AI (230), pharmacovigilance explainable ML (181), and pharmacovigilance explainable machine learning (213).

3. **10 J. Rebane, I. Samsten, P. Pantelidis, and P. Papapetrou, ''Assessing the clinical validity of attention-based and SHAP temporal explanations for adverse drug event predictions,'' in Proc. IEEE 34th Int. Symp. Comput. Based Med. Syst. (CBMS), Jun. 2021, pp. 235–240.:**

There has been a surge in XAI studies in drug-related applications since 2019, with relatively few studies from 2013 to 2021. The limited number of publications indicates a demand for more research on XAI in PV applications.

4. **A. S. Mantripragada, S. P. Teja, R. R. Katasani, P. Joshi, and R. Ramesh, ''Prediction of adverse drug reactions using drug convolutional neural networks,'' J. Bioinf. Comput. Biol., vol. 19, no. 1, Feb. 2021, Art. no. 2050046, doi: 10.1142/S0219720020500468.:**

These search terms were used in a Google Scholar search on 22 June 2021, and the numbers in parentheses are the number of articles returned from each search. Retrieved articles were first screened for titles and abstracts to exclude duplicates, then articles were added through a first full-text review for relevance and a second full-text review based on a selective methodology, resulting in a final selection of 25 unique publications

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III. METHODOLOGY

Data Collection and Integration:

This methodology involves gathering diverse sources of structured and unstructured data relevant to pharmacovigilance, such as electronic health records, adverse event reports, drug labels, clinical trial data, and scientific literature. Each data source may have varying formats, standards, and levels of granularity. Data integration techniques are then applied to unify these heterogeneous data into a standardized format suitable for analysis. This process ensures that all relevant information is captured and made available for AI model training and evaluation.

Data Preprocessing and Cleaning:

Before analysis, the collected data must undergo preprocessing to address issues such as missing values, outliers, noise, and inconsistencies. Data cleaning techniques, including imputation, normalization, and outlier detection, are applied to ensure data quality and consistency. This step is crucial for improving the reliability and accuracy of AI models by ensuring that they are trained on clean and consistent data.

Feature Engineering:

Feature engineering involves selecting, transforming, and creating new features from the raw data to improve the performance of AI models. This process may include techniques such as feature selection, dimensionality reduction, and the creation of domain-specific features. Feature engineering aims to capture the most relevant information from the data while reducing noise and redundancy, thereby enhancing the interpretability and predictive power of the AI models.

Data Augmentation:

Data augmentation techniques are used to increase the size and diversity of the training data by generating synthetic samples or perturbing existing data points. This helps improve the generalization and robustness of AI models, especially when dealing with limited or imbalanced data. Data augmentation methods such as rotation, translation, flipping, and adding noise can help create a more comprehensive representation of the underlying data distribution, leading to more reliable and interpretable model outputs.

Data Privacy and Security:

Given the sensitive nature of healthcare data, data methodologies must prioritize privacy and security throughout the data lifecycle. Techniques such as anonymization, encryption, access control, and compliance with data protection regulations (e.g., GDPR, HIPAA) are essential to safeguard patient confidentiality and prevent unauthorized access or misuse of sensitive information. By adopting rigorous data privacy and security measures, XAI applications in pharmacovigilance can build trust and confidence among stakeholders while ensuring compliance with regulatory requirements

Model Architecture:

The system architecture for an explainable AI application in pharmacovigilance typically involves data ingestion from various sources such as electronic health records and adverse event databases. Preprocessing steps like data cleaning and feature engineering are performed, followed by model training using interpretable algorithms. Post-processing techniques are applied for explanation generation. The architecture includes components for model deployment, integration with existing pharmacovigilance systems, and a user interface for healthcare professionals to access and interpret AI-driven insights, ensuring transparent and actionable information for patient safety monitoring.

Decision tree classifiers:

Instead Decision tree classifiers are used successfully in many diverse areas. Their most important feature is the capability of capturing descriptive decision making knowledge from the supplied data. Decision tree can be generated from training sets.

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Gradient boosting:

Gradient boosting is a machine learning technique used in regression and classification tasks, among others. It gives a prediction model in the form of an ensemble of weak prediction models, which are typically decision trees.[1][2] When a decision tree is the weak learner, the resulting algorithm is called gradient-boosted trees; it usually outperforms random forest .A gradient-boosted trees model is built in a stage-wise fashion as in other boosting methods, but it generalizes the other methods by allowing optimization of an arbitrary differentiable loss function.

K-Nearest Neighbors (KNN):

It The k-Nearest Neighbors (KNN) algorithm is a straightforward and intuitive machine learning method used for classification and regression tasks. It operates on the principle of similarity, where the classification or prediction of a data point is determined by the majority vote or averaging of its k nearest neighbors in the feature space.

In kNN classification, when presented with a new data point, the algorithm calculates its distance to all other points in the training dataset using a chosen distance metric, commonly Euclidean distance. Then, it selects the k nearest neighbors based on these distances. The class of the new data point is then determined by the majority class among its k neighbors.

For regression tasks, KNN similarly identifies the k nearest neighbors of a data point but instead computes the average or weighted average of the target values of these neighbors to predict the target value of the new data point.

kNN is a non-parametric and lazy learning algorithm, meaning it does not make any assumptions about the underlying data distribution and does not require training a model before making predictions. However, its performance can be sensitive to the choice of k and the distance metric, and it can be computationally expensive for large datasets since it requires storing and searching through the entire training dataset for each prediction. Nonetheless, kNN remains popular due to its simplicity and effectiveness in many classification and regression tasks.

Random Forest:

Random forests or random decision forests are an ensemble learning method for classification, regression and other tasks that operates by constructing a multitude of decision trees at training time. For classification tasks, the output of the random forest is the class selected by most trees. For regression tasks, the mean or average prediction of the individual trees is returned. Random decision forests correct for decision trees' habit of overfitting to their training set. Random forests generally outperform decision trees, but their accuracy is lower than gradient boosted trees. However, data characteristics can affect their performance.

The first algorithm for random decision forests was created in 1995 by Tin Kam Ho[1] using the random subspace method, which, in Ho's formulation, is a way to implement the "stochastic discrimination" approach to classification proposed by Eugene Kleinberg.

An extension of the algorithm was developed by Leo Breiman and Adele Cutler, who registered "Random Forests" as a trademark in 2006 (as of 2019, owned by Minitab, Inc.).The extension combines Breiman's "bagging" idea and random selection of features, introduced first by Ho[1] and later independently by Amit and Geman to construct a collection of decision trees with controlled variance.

Random forests are frequently used as "blackbox" models in businesses, as they generate reasonable predictions across a wide range of data while requiring little configuration.

Logistic regression Classifiers:

Logistic regression analysis studies the association between a categorical dependent variable and a set of independent (explanatory) variables. The name logistic regression is used when the dependent variable has only two values, such as 0 and 1 or Yes and No. The name multinomial logistic regression is usually reserved for the case when the dependent variable has three or more unique values, such as Married, Single, Divorced, or

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Widowed. Although the type of data used for the dependent variable is different from that of multiple regression, the practical use of the procedure is similar.

This program computes binary logistic regression and multinomial logistic regression on both numeric and categorical independent variables. It reports on the regression equation as well as the goodness of fit, odds ratios, confidence limits, likelihood, and deviance. It performs a comprehensive residual analysis including diagnostic residual reports and plots. It can perform an independent variable subset selection search, looking for the best regression model with the fewest independent variables. It provides confidence intervals on predicted values and provides ROC curves to help determine the best cutoff point for classification. It allows you to validate your results by automatically classifying rows that are not used during the analysis.

Naïve Bayes:

The naive bayes approach is a supervised learning method which is based on a simplistic hypothesis: it assumes that the presence (or absence) of a particular feature of a class is unrelated to the presence (or absence) of any other feature .

Yet, despite this, it appears robust and efficient. Its performance is comparable to other supervised learning techniques. Various reasons have been advanced in the literature. In this tutorial, we highlight an explanation based on the representation bias. The naive bayes classifier is a linear classifier, as well as linear discriminant analysis, logistic regression or linear SVM (support vector machine). The difference lies on the method of estimating the parameters of the classifier (the learning bias).

While the Naive Bayes classifier is widely used in the research world, it is not widespread among practitioners which want to obtain usable results. On the one hand, the researchers found especially it is very easy to program and implement it, its parameters are easy to estimate, learning is very fast even on very large databases, its accuracy is reasonably good in comparison to the other approaches. On the other hand, the final users do not obtain a model easy to interpret and deploy, they do not understand the interest of such a technique.

Thus, we introduce in a new presentation of the results of the learning process. The classifier is easier to understand, and its deployment is also made easier. In the first part of this tutorial, we present some theoretical aspects of the naive bayes classifier. Then, we implement the approach on a dataset with Tanagra. We compare the obtained results (the parameters of the model) to those obtained with other linear approaches such as the logistic regression, the linear discriminant analysis and the linear SVM. We note that the results are highly consistent. This largely explains the good performance of the method in comparison to others. In the second part, we use various tools on the same dataset (Weka 3.6.0, R 2.9.2, Knime 2.1.1, Orange 2.0b and RapidMiner 4.6.0). We try above all to understand the obtained results.

SVM:

In classification tasks a discriminant machine learning technique aims at finding, based on an independent and identically distributed (iid) training dataset, a discriminant function that can correctly predict labels for newly acquired instances. Unlike generative machine learning approaches, which require computations of conditional probability distributions, a discriminant classification function takes a data point x and assigns it to one of the different classes that are a part of the classification task. Less powerful than generative approaches, which are mostly used when prediction involves outlier detection, discriminant approaches require fewer computational resources and less training data, especially for a multidimensional feature space and when only posterior probabilities are needed. From a geometric perspective, learning a classifier is equivalent to finding the equation for a multidimensional surface that best separates the different classes in the feature space.

SVM is a discriminant technique, and, because it solves the convex optimization problem analytically, it always returns the same optimal hyperplane parameter—in contrast to genetic algorithms (GAs) or perceptrons, both of which are widely used for classification in machine learning. For perceptrons, solutions are highly dependent on the initialization and termination criteria. For a specific kernel that transforms the data from the input space to the feature space, training returns uniquely defined SVM model parameters for a given training set, whereas the perceptron and GA classifier models are different each time training is initialized. The aim of

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GAs and perceptrons is only to minimize error during training, which will translate into several hyperplanes' meeting this requirement.

Splitting the dataset into training and testing sets:

The dataset is then split into two parts: a training set and a testing set. The training set is used to train the machine learning model, and the testing set is used to evaluate the performanceof the trained model.

MODEL TRAINING AND EVALUATION:

- Train the model
- Tune Hyperparameters
- Evaluate model based on Accuracy, Precision, Recall, F1 Score.

Deployment:

Deploy the trained model

Model Evaluation:

Evaluate the model's performance using accuracy, precision, recall, f1 score and confusion matrix. The confusion matrix table shows model performance by comparing actual values of the data with predicted values. It gives a more detailed picture of how well the model is performing by showing the number of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). True positives (TP) are the cases where the model correctly predicted a positive outcome (the student was dropped out) when the case was positive (the student was dropped out of college).

True negatives (TN) are the cases where the model correctly predicted a negative outcome (the student was not dropped out) when the actual case was negative (the student was not dropped out of college).

False positives (FP) are the cases where the model predicted a positive outcome (the student was dropped out) when the actual case was negative.

False negatives (FN) are the cases where the model predicted a negative outcome (the student was not dropped out) when the actual case was positive.

Architecture:

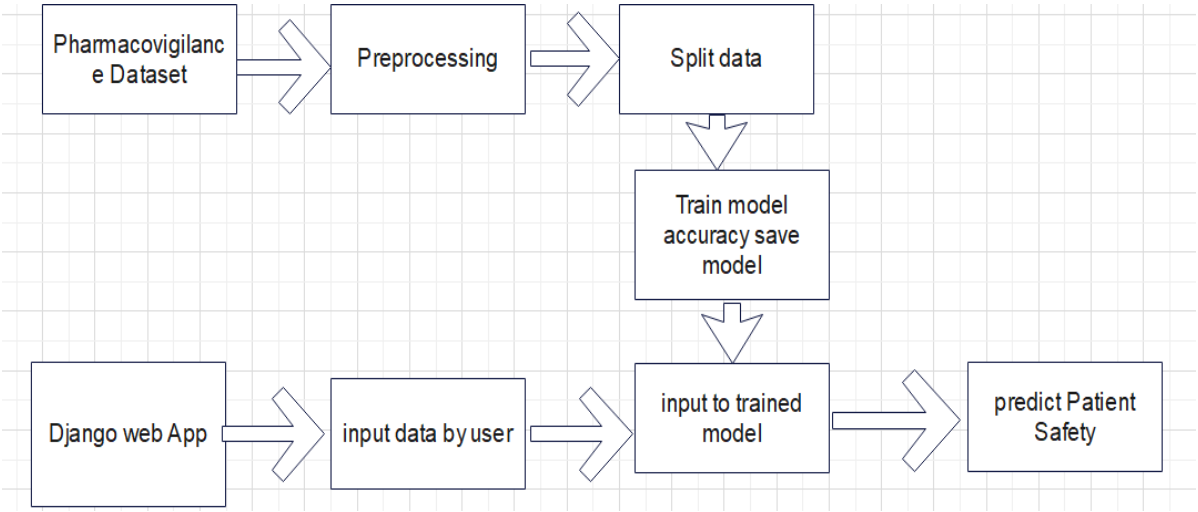

Fig 1: Flow chart of Methodology

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IV. RESULT AND ANALYSIS

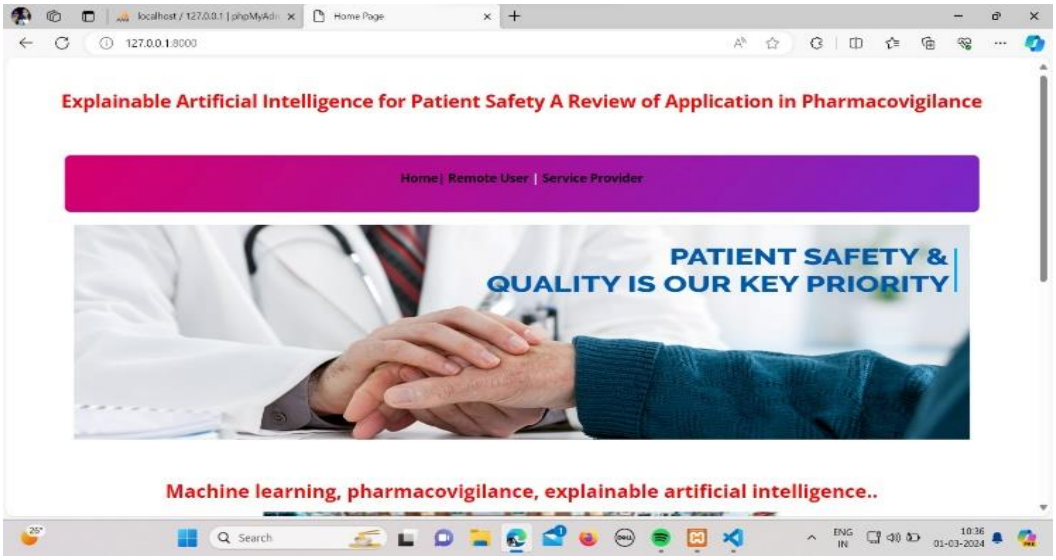

Fig 2: Home Page

Fig 3: Login page

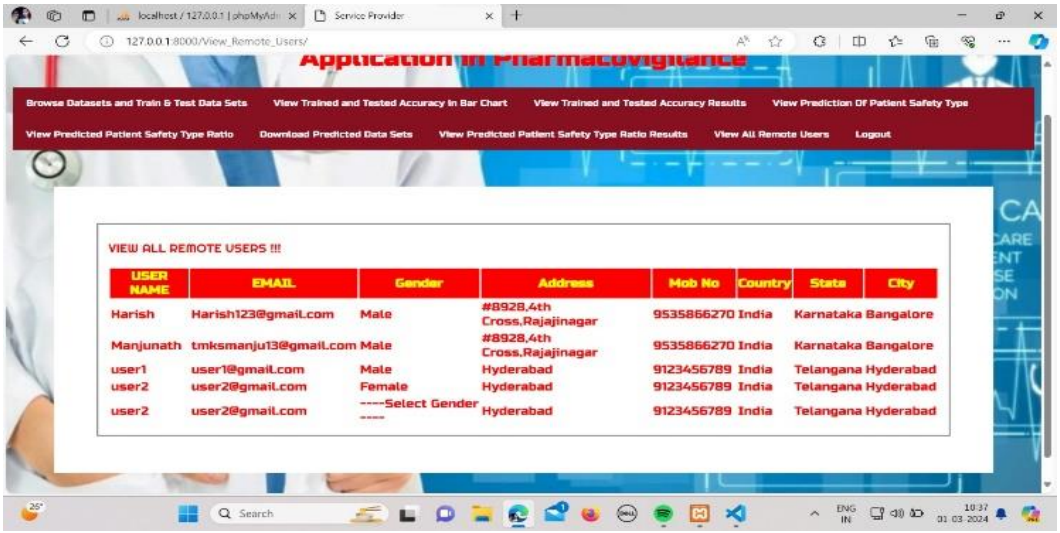

Fig 4: List of remote users

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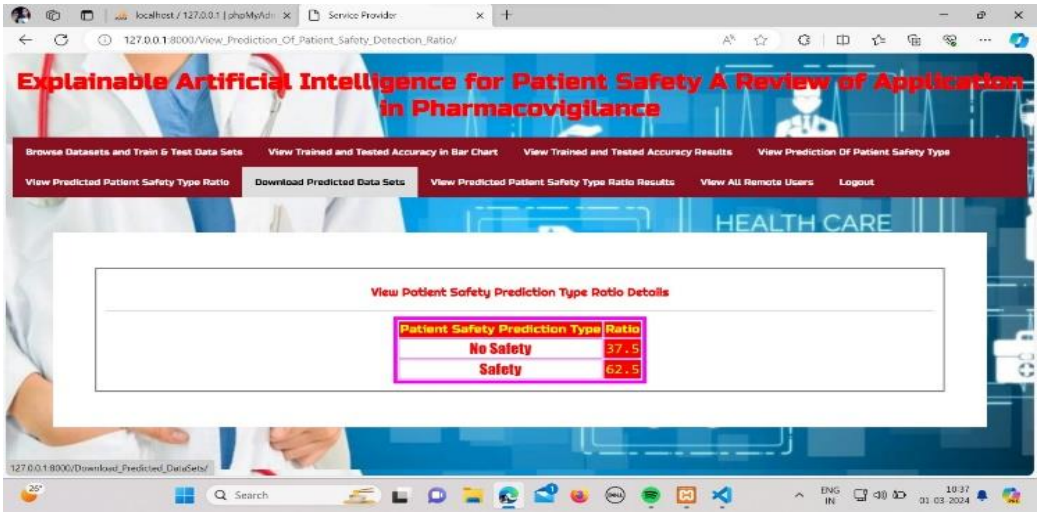

Fig 5: Prediction type ratio details

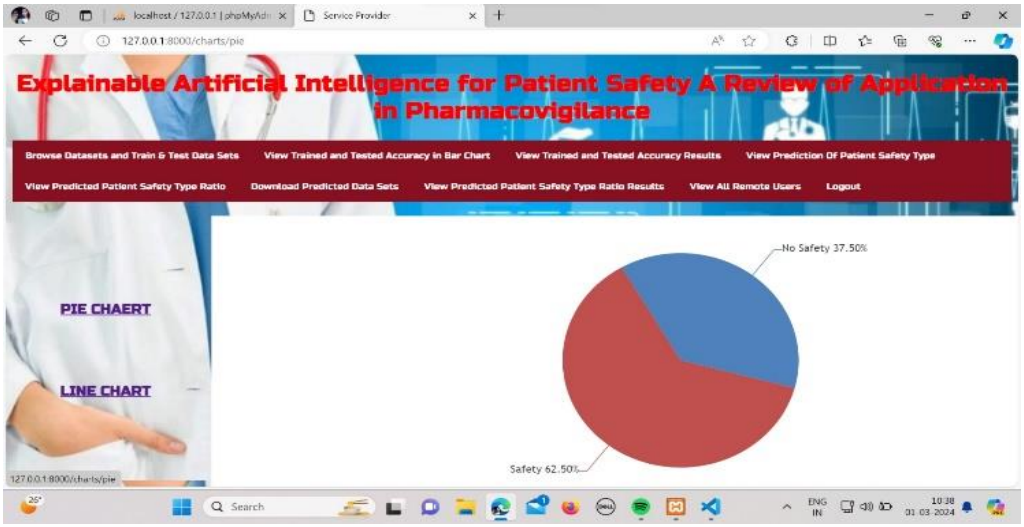

Fig 6: Pie Chart view of train and tested accuracy

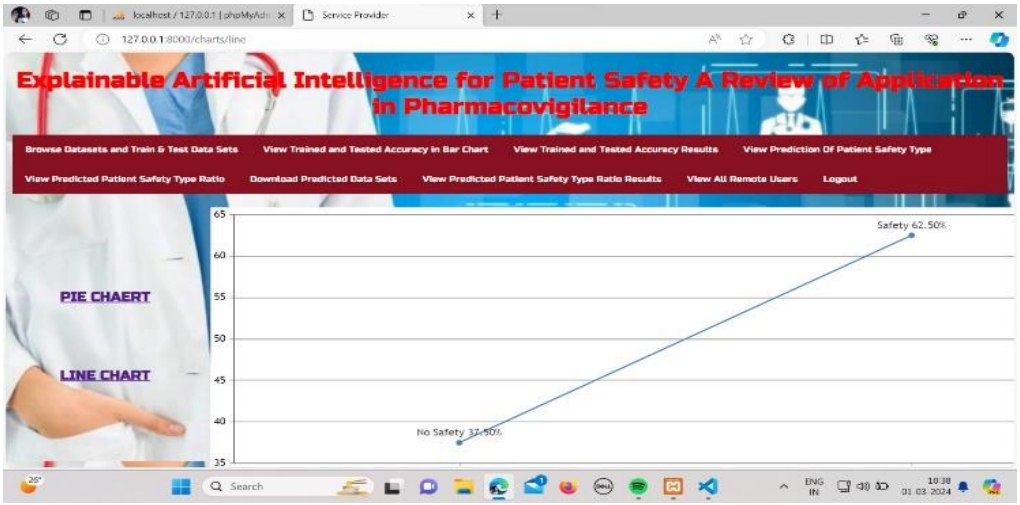

Fig 7: Logistic Regression View

V. CONCLUSION

In this study, we reviewed PV XAI papers and discussed recent research trends and the need for XAI research. Unlike other areas where XAI and AI are developing together, PV XAI research is still in its infancy. There are

not many papers on PV XAI and the methodology is limited to a few models. However, studies are slowly beginning to show the potential of XAI research for medication monitoring and patient safety, collecting ADR and ADE information, extracting drug-drug interactions, and predicting drug treatment effects.

As in other areas, as awareness of XAI methods grows, we expect to see AI used in pharmacovigilance and patient safety in many more ways in the coming years than those identified in this review, and the positive potential of XAI for drug therapy, ADRs and interactions is very promising. However, it is clear that the growth of this field may be limited by the lack of validated and established uses of XAI in real-world healthcare settings, and this is an area that requires further investigation. Therefore, the challenges and future prospects of XAIs in pharmacovigilance should be discussed with continued interest.

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