Review of Immunotherapy Classification: Application Domains, Datasets, Algorithms and Software Tools from Machine Learning Perspective

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***Abstract*—Immunotherapy treatments can be essential sometimes and a waste of valuable resources in other cases, depending on the diagnosis results. Therefore, researchers in immunotherapy need to be updated on the current status of research by exploring: application domains e.g. warts, datasets e.g. immunotherapy, classifiers or algorithms e.g. *k*NN and software tools. The research objectives were: 1) to study the immunotherapy-related published literature from a supervised machine learning perspective. In addition, to reproduce immunotherapy classifiers reported in research papers. 2) To find gaps and challenges both in publications and practical work, which may be the basis for further research. Immunotherapy, diabetes, cryotherapy, exasens data and "one unbalanced dataset" are explored. The results are compared with published literature. To address the found gaps in further research: novel experiments, unbalanced studies, focus on effectiveness and a new classifier algorithm are suggested.**

I. INTRODUCTION

In immunotherapy, a skin test antigen is injected into a lesion, resulting in a T-cell-mediated immune response. The immunotherapeutic treatment method leads to a more apparent immune reaction. Immunotherapy is a promising therapeutic approach in healthcare as it strengthens the immune system and enables the patient to resist [1]. However, it is impossible to find patterns in the data by visual scanning [2]. To solve this issue, machine learning is essential to draw useful conclusions from the raw data [3]. This may be necessary for healthcare to treat a disease, due to the level of analysis and the nature of the data.

A sub-field of artificial intelligence [4], machine learning plays an essential role in finding successful classification of medical therapies for diseases. Classification can be defined as finding unidentified observations by learning already existing patterns. Classification is challenging in medical applications, for example, distinguishing immunotherapy treatments for healthcare professionals because the datasets are difficult to understand [5], analyse and interpret by looking at the data with an ordinary eye only [6]. Data mining algorithms such as Decision Tree, Random Forest, Naive Bayes, *k*NN, and Gradient Boost tree, are commonly used to predict disease or a health treatment [7]. Algorithms can be developed for classification and these are used to achieve reasonable results in knowledge extraction. Several researchers have studied the utilisation of predictive algorithms for treatments' selection for warts diseases [5] [8] [9] [10] [11], to enhance medical diagnosis and reduce subjective bias in doctors' decision making. For example, the research papers developed algorithms to find a better treatment either immunotherapy or cryotherapy.

Immunotherapy research faces obstacles because it is archived in databases, publications and research reports in different formats, degrees of difficulty, quality and quantity [12]. Health applications today generate a large amount of data. The challenge, however, is to transform data into a decision-making system using advanced information technologies, as traditional systems struggle to adapt and keep up with developments [13]. Clinicians collect data most conveniently, regardless of whether the data can be aggregated and analysed. The problem is converting raw data into useful information about immunotherapy by striking a balance and bridging the gap between the knowledge gap and the application gap. In addition, health professionals have difficulty understanding research because some details are missing; for example, the code and tools. Some studies did not explore the unbalanced immunotherapy data thoroughly and did not mention the most essential parameters of sensitivity and specificity as well as the utilised tools.

Immunotherapy datasets are usually unbalanced and small making the process of implementing the machine learning algorithms suboptimal. Therefore, a study is conducted proposing novel machine learning experiments based on strategies for the classification of unbalanced datasets "in press" [14]. In another research personalised and adaptable novel machine experiments are performed to simulate and prepare the data before algorithm implementations "in press" [15]. Furthermore, a novel algorithm Pareto Principle is introduced and applied for the classification of small biomedical health-related datasets based on multi-objective optimisation and ABC analysis "in press" [16].

The contribution of this paper is to perform a literature review to be updated on the current status of research to study research development regarding immunotherapy. Application domains in health care e.g. heart disease, datasets e.g. immunotherapy [17], algorithms e.g. Random Forest and software tools will be explored. To find out the strong points and weaknesses of the publications, four research articles are selected from the research literature CÜvitoğlu and Işık (2018) [18]; Rahman et al., (2020) [19]; Fazriansyah et al., (2020) [20]; and Akben, (2018) [5]. A common view of this selected research is that research papers analyse both immunotherapy and cryotherapy datasets. Immunotherapy [17], diabetes [21], cryotherapy [22], exasens data [23] and ”one unbalanced dataset” [24] will be used as case studies. The datasets are chosen based on availability, manageability and understandability. The objective is to explore the published literature and reproduce some algorithms implemented by research papers, to find gaps and challenges both in published literature and in experimental work, which will be the basis for further research. The supervised approach of classification will be considered when classifying the datasets. Experimental work will be performed classifying the datasets applying Bayes Network, J48 (C4.8 decision trees based), *k*NN, ZeroR, Serialised Classifier, Multi Scheme, Artificial Neural Network and Random Forest. The results will be compared with published literature. Data analysis tools of Weka and Python will be used.

The rest of the paper is structured as follows: the second section illustrates various domains of immunotherapy. The third section introduces immunotherapy related datasets. The fourth section describes algorithms or classifiers used by researchers. The fifth section shows the tools used by other research papers. The sixth section presents the gaps in publications. The seventh section is about addressing selected research papers. The eighth section presents the reproduction of algorithm implementations in research papers, classifying the datasets. Additionally comparison of applied algorithms with published literature. The remaining sections are discussion, conclusion and future perspectives.

II. APPLICATION DOMAINS

Immunotherapy is frequently used in healthcare domains such as warts, these are covered in the paragraphs below. Table I demonstrates various authors' algorithm implementations.

TABLE I
ALGORITHMS DEVELOPMENTS IN IMMUNOTHERAPY

Implementations		
Algorithmn	Publication	Disease
Fuzzy Neural Network algorithm	Guimaraes et al. (2019), [9]	Warts
Feed-forward Neural Network	Rajeswari et al., (2012) [25]	Heart disease
Random Forest, kNN and AdaBoost	Khan (2015) [26]	Parkinson's
Decision tree	Yeh et al., (2011) [27]	Hemodialysis
C4.5	Zayed et al., (2013) [28]	Liver disease
CART	Breault et al., (2002) [29]	Diabetes

Heart disease can lead to heart attack, but 90% of cardiovascular disease (CVD) is preventable [13]. When it comes to detecting CVDs early, a lot of research is done using data mining tools. Cardiovascular disease can lead to heart attack due to blockage of blood vessels. A system for the diagnosis of cardiac risk factors is presented by Jonnagaddala et al., (2015) [30]. Rajeswari et al., (2012) [25] demonstrated feature selection using a feed-forward neural network for ischemic heart disease detection, reducing the feature set from 17 to 12 and increasing accuracy from 82.2% to 89.4%.

Parkinson's disease (PD) is a multisystem neurodegenerative and affects the motor system. PD amplifies the characteristic motor disturbances [31], Slowing of movement and inactive tremor. Various classifiers are used and compared by Little et al. (2007) [32] for example (decision tree, neural networks and regression tree) on the Max Little dataset for PD detection. The study showed that the neural network achieves a classification accuracy of 92.9%. In another study, Khan (2015) [26] used Random Forest, *k*NN and AdaBoost to diagnose Parkinson's patients. The study concludes that *k*NN achieves an accuracy of 90.26%.

Cost reduction is an important factor, as the cost of care for end-stage hemodialysis patients is high. Approximately 50 features are observed in kidney dialysis treatment, then many aspects can affect the patient's probability of survival [33]. To better understand the implications of data mining, it can be helpful to understand the domain before analysing the data. Data mining techniques (minimum multiple support association rule and decision tree) and temporal abstraction have been used by Yeh et al. (2011) [27] to examine the biochemical data of dialysis patients. The study discovered a decision support system that aims to arrive at models that lead to patient hospitalization.

Early diagnosis of patients is often an inevitable obstacle. Kusiak et al. (2005) [33] used two different decision rule techniques to generate insights that are then used to predict patient survival probability. To reveal the risk aspects of pressure ulcers, Raju et al. (2015) [34] implemented different classifiers, such as decision trees and Random Forest. By comparison, Random Forest performed best.

One of the most important reasons for hospitalization is stroke. Recognizing the stage of stroke and identifying risk can facilitate prevention. Khosla et al., (2010) [35] carried out an automatic feature selection algorithm. The method selected robust features and evaluated three automatic feature extraction strategies: conservative mean feature selection (CM), regular logistic regression (RLR), and advanced feature selection (FSS). Margin-based censored regression (MCR) and SVM are used for classification. The study concluded that the MCR achieved the best accuracy, in this case, using the conservative averaging method.

Liver disease is impaired liver function and can lead to disease. Usually, symptoms of liver disease do not appear until the liver becomes dysfunctional and the disease is incurable. However, if liver disease is caught early, the severely damaged liver can be reversed and treated. The decision tree (C4.5) was used to classify patients with HCV (Zayed et al., 2013) [28].

Many authors have researched to diagnose diabetes, multiple diseases are associated with diabetes due to the low production of insulin by the pancreas. There are many datasets to explore.

CART is proposed by Breault et al., (2002) [29] applied to diabetics and shown that age is the most important characteristic linked to glycemic control in the body.

Akben (2018) [5] established an ID3 decision tree classification to predict the choice of treatment options for warts for immunotherapy and cryotherapy. Khatri et al., (2018) [10] presented a J48 resolution. Khozeimeh et al., (2017) [8] introduced an expert system based on unclear logical rules for studying the therapeutic response of immunotherapy and cryotherapy treatments on warts of skin. To improve the accuracy of the model prediction, Guimaraes et al., (2019) [9] applied the fuzzy neural network algorithm.

III. DATASETS

To classify the datasets better and obtain reasonable results, studying other immunotherapy-related datasets is useful. Some immunotherapy datasets mentioned by immunotherapy related publications are indicated in the following: immunotherapy [17], diabetes [21], cryotherapy [22], exasens data [23], B-cell data [36] and sample serum [37].

A. Immunotherapy and Cryotherapy

The datasets, immunotherapy and cryotherapy, originally published by Khozeimeh et al., [8] are available in the UCI Machine Learning Repository [19]. Many research publications examined immunotherapy and cryotherapy datasets together in the research literature, this study will also consider these datasets. The data was collected over two years, from January 2013 to February 2015, in a dermatological clinic. Patients with plantar and vulgar warts over 15 years of age were treated with immunotherapy or cryotherapy treatments. A total of 180 patients were randomly divided into two groups of equal size, group A and group B. Patients in group A were treated with immunotherapy by intralesional injection of Candida antigen, while patients in group B were treated with liquid nitrogen cryotherapy. The mode of immunotherapy treatment consisted of a maximum of three sessions with an interval of three weeks between two consecutive sessions. The cryotherapy method of treatment, on the other hand, provided for a maximum of ten sessions with a break of one week between two consecutive sessions. The results of the treatment methods were recorded in the datasets with a range of clinical and demographic characteristics of the patients. The immunotherapy dataset contains 90 observations with 8 attributes, while the cryotherapy dataset contains 90 observations with 7 attributes. The response variable for both datasets is result-of-treatment, see Table II.

TABLE II
STATISTICAL DETAILS OF THE IMMUNOTHERAPY DATASET. NOTE: *THE TIME BEFORE COMMENCEMENT OF THE TREATMENT. **THE LARGEST WART'S SURFACE AREA. SD (STANDARD DEVIATION), MM (MILLIMETER), CA. (CATEGORICAL), NU. (NUMERICAL), PL. (PLANTAR), CO. (COMMON)

Number	Attributtes	Kind	Immunotherapy Results	
			Quantity	**Mean /SD**
1	Gender	Ca.	Male (41) Female (49)	
2	Age (years)	Nu.	15-56	31.04/12.23
3	*Time	Nu.	0-12	7.23/3.10
4	Number of warts	Nu.	1-19	6.16/4.2
5	Type of warts	Ca.	Pl. (22) Co. (47) Both (21	
6	** Area (mm^2)	Nu.	6-900	95.7/136.61
7	Induration (mm)	Nu.	2-70	14.33
8	Success of treatment	Ca.	Yes (71) No (19)	

B. Cryotherapy

Some research papers analysed immunotherapy and cryotherapy datasets simultaneously [5] [8] [9] [10], The cryotherapy dataset consists of 90 observations, of which 42 are negative diagnosed and 48 are positive as in Table III. The cryotherapy dataset is balanced; the percentage of the output variable, result-of-treatment are approximately the same 53.3% for successful treatment and 46.7% for unsuccessful treatment [19]. The percentage of successful treatments is higher. However, the treatment was not successful for many patients in this case.

TABLE III
EXPLANATORY STATISTICS FOR CLINICAL ATTRIBUTES OF THE CRYOTHERAPY DATASET

#	Attributes	Kind	Cryotherapy Treatments	
			Quantity	**Mean / SD**
1	Gender	Categorical	Male (47) Female (43)	- -
2	Age (years)	Numerical	15-67	28.6 / 13.36
3	Time	Numerical	0-12	7.66 / 3.4
4	Number of warts (count)	Numerical	1-12	5.51 / 3.57
5	Type of warts	Categorical	Plantar (9) Common (54) Both (27)	- - -
6	Area (mm^2)	Numerical	4-750	85.83 / 131.73
7	Treatment succeeded	Categorical	Yes (48) No (42)	- -

C. Exasens Data

The Exasens dataset is open source and can be downloaded from the UCI machine learning repository [38]. The dataset can be used to examine the classification of healthy controls (HC) and saliva samples from patients with COPD and asthma. The dataset contains information on saliva samples collected from four groups of respiratory patients, including COPD (40 samples), HC (40 samples), patients with respiratory infections without COPD or asthma (10 samples), and asthma (10 samples). The dataset contains attributes related to patient demographics (gender, smoking status and age) and patient classification is based on these.

D. Sample Serum

Cross-sectional survey: One hundred and seventy-eight serum samples were obtained from a cross-sectional population survey (1-75 years) [37]. These sera were collected in October 1988 during the malaria transmission season.

Longitudinal section: At the beginning of the malaria transmission season (May 1988), plasma samples were collected from 355 children between the ages of 3 and 8. For the next six months, each child was seen once a week by a field worker to assess their clinical status. Blood smears were taken from all children who had a fever or an armpit temperature of 37.5 ° C and examined for malaria parasites. The children were re-examined in November at the end of the malaria transmission season and a finger sample was taken and examined for malaria parasites. With this information, it was possible to classify each child's experience of malaria over the previous six months. For the study, only children who had a clinical episode of malaria (fever plus parasitaemia 5,000 parasites / L of blood) or an asymptomatic disease infection of the child (cross-sectional or increased parasemia spleen size during the transmission season if no clinical symptoms occurred at any time during the previous 6 months were included in the analysis.) Those who showed no signs of infection during follow-up or cross-sectional investigations were not included because it could not be said whether they were truly resistant to infection, did not detect asymptomatic infection, or simply had not been detected. . of being bitten by a contagious mosquito. **Control sera**: Control sera (n 50 for cross-sectional analysis, n 15-20 for IgG subclass analysis of cross-sectional samples, n 40 for longitudinal analysis) were obtained from donors without exposure before malaria see Table IV.

TABLE IV
ILLUSTRATING THE SAMPLE SERA AND CONTROL SERA OF THE SAMPLE SERUM DATA

Sample Sera		**Control Sera**	
Cross-sectional survey	Longitudinal section	Cross-sectional survey	Longitudinal section
178 (1-75 years)	355 (3-8 years)	50	40

E. B-cell Data

B-cell data is selected for this study. B- cells are immune cells that recognize antigens when producing antibodies [36]. Antibodies can inhibit the function of antigen proteins by binding to antigen epitope regions. Hence, it is very helpful to find a good prediction model of the epitope for this problem. There are some physical methods to predict the epitope. For instance, the three-dimensional structural analysis of antibody-antigen complexes by X-ray or nuclear magnetic resonance (NMR) spectroscopy is considered to identify the epitope, see Table V.

TABLE V
DISPLAYING INDEPENDENT AND DEPENDENT FEATURES OF THE B-CELL DATA

Independent variables	Dependent variable:
(i) start position: start position of peptide	(i) Antibody valence (target value)
(ii) end position: end position of peptide	
(iii) chou fasman: peptide feature, turn	
(iv) emini: peptide feature, relative surface accessibility	
(v) kolaskar tongaonkar: peptide feature, antigenicity	
(vi) parker: peptide feature	
(vii) isoelectric point: protein feature	
(viii) aromaticity: protein feature	
(ix) hydrophobicity: protein feature	
(x) stability: protein feature	

IV. ALGORITHMS

Medical professionals often select treatment methods using personal experience and medical knowledge, however, this prediction based on the senses may not be optimal [5] [39]. Furthermore, the success rate of sensory procedures has not been proved statistically and it is not easy for medical professionals to decide on a treatment. Therefore, in recent research, computer-assisted automated prediction methods (machine learning data mining algorithms) have been recommended, which are already used for the treatment of several diseases such as warts [40] [8].

In this section, research papers' application of algorithms on immunotherapy dataset [17] will be considered. The immunotherapy dataset has eight features: time, induration-diameter, age, number-of-warts, area, type, gender and result-of-treatment. However, the result-of-treatment is the output variable, and the other attributes are input variables. A categorical output variable represents a classification predictive modelling challenge.

A. Random Forest And kNN

Table VI shows the accuracy, sensitivity and specificity of *k*-Nearest Neighbours algorithm and Random Forest implementations classifying the immunotherapy dataset by Rahman et al., (2020) [19] as well as CÜvitoğlu and Işik, (2018) [18]. Implementing Random Forest, Rahman et al., (2020) obtained better classification results (accuracy of 92.7% specificity of 84.8% and sensitivity of 95.1%) than CÜvitoğlu and Işik, (2018). Random Forest outperformed the *k*-Nearest Neighbours algorithm in the case of both publications. The difference in the results obtained may be the difference in preprocessing of the data before algorithm implementations. In addition, the algorithms select the subsets of input variables randomly, which may affect the output.

TABLE VI
IMPLEMENTATION RESULTS OF *k*-NEAREST NEIGHBOURS ALGORITHM AND RANDOM FOREST ON IMMUNOTHERAPY DATASET REVEALED IN RESEARCH LITERATURE

Algorithm	Accuracy	Specificity	Sensitivity
Random Forest			
Rahman et al., (2020) [19]	92.7%	84.8%	95.1%
CÜvitoğlu and Işik, (2018) [18]	88%	50%	99%
***k*-Nearest Neighbours Algorithm**			
Rahman et al., (2020) [19]	80.9%	93.6%	78.1%
CÜvitoğlu and Işik, (2018) [18]	61%	10%	74%

B. Structural Overview

The usage of algorithms by research papers is indicated in Table VII. For example, Giumaraes et al. (2019) [9] and Rahman et al., (2020) [19] utilised Neural Networks and Support Vector Machines respectively to analyse and classify the datasets.

TABLE VII
DEMONSTRATION OF RESEARCH PAPERS' UTILISATION OF VARIOUS ALGORITHMS TO CLASSIFY THE TREATMENTS OF ON IMMUNOTHERAPY DATASET OF WARTS

Immunotherapy	
Algorithmn	Publication
Linear:	
Neural Networks	Giumaraes et al., (2019) [9]
Decision Tree-based Rules	Akben (2018) [5]
Both Linear and Non-linear:	
Support Vector Machines	Rahman et al., (2020) [19]
Random Forest and others	CÜvitoğlu and Işik (2018) [18]
Ensamble:	
AdaBoost and Random Forest	Putra et al., (2018) [41]
Others:	
Rules-based Fuzzy Logic	Khozeimeh et al., (2017) [8]

In the sections underneath machine learning algorithms are organised as non-linear, a combination of linear and non-linear, ensemble methods as well as other algorithms.

1) Applications of Non-linear Algorithms: Guimarães et al., (2019) [9] concluded that the hybrid approach based on neural networks and fuzzy systems could contribute enormously to a better classification of the assessment of immunotherapeutic treatments. Eventually, these methods can improve the ability of health professionals to treat patients successfully. Acceptable accuracy, sensitivity and specificity of 88.6%, 93.0% and 86.0%, respectively, are achieved. The hybrid method is useful for extracting knowledge from the dataset and increasing the accuracy of the classification. Fazriansyah et al., (2020) [20] implemented the neural network algorithm in another study to analyse the immunotherapy dataset with the aim of better classification accuracy. The details of the neural network are as follows: data training cycles = 200, moment = 0.9, learning levels = 0.01. Neural network obtained a reasonable accuracy of 80% and AUC of 0.738, high accuracy and AUC mean that the immunotherapy dataset falls into the medium classification category. The immunotherapy dataset can be used as a benchmark for evaluating the success of immunotherapeutic treatments.

Akben, (2018) [5] concluded that the selection of a treatment method is a challenge, as success depends on proper treatments and the patient. In this study, decision tree-based rules are used to predict the success of cryotherapy and immunotherapy treatments for warts. Classification performance obtained an accuracy of 90% for immunotherapy and 94.4% for cryotherapy treatments. To understand the success rate of the treatments, the decision rules are converted into images and the performance is displayed as a function of the age of the patient and the time elapsed since the presence of the disease. Ghiasi and Zendehboudi, (2019) [42] applied the Classification and Regression Trees (CART) method to cryotherapy and immunotherapy treatments for plantar and common warts to select a suitable treatment. The assessment performance of CART demonstrated accuracy, sensitivity, and specificity of 100% for datasets of cryotherapy and immunotherapy.

2) Deployments of both Non-linear and Linear Algorithms: Rahman et al., (2020) [19] applied the Support Vector Machine (SVM) using cryotherapy and immunotherapy datasets. The patients who suffered from various types of warts received both cryotherapy and immunotherapy treatments. The immunotherapy dataset is unbalanced and three different oversampling methods are used to balance the classes, namely borderline SMOTE, adaptive synthetic sampling (ADASYN), and synthetic minority oversampling technique (SMOTE). A sequential selection algorithm (SBS) is used to select the optimal set of attributes. In immunotherapy treatment, SVM with radial-based core function (RBF) achieved an overall classification accuracy, sensitivity and specificity of 94.6%, 96.0% and 89.5%, respectively. In cryotherapy treatment, SVM with the polynomial kernel achieved an accuracy of 95.9% (sensitivity = 96.0%, specificity = 89.5%).

CÜvitoğlu and Işik (2018) [18] implemented several machine learning algorithms to select a suitable wart treatment algorithm. Random Forest (RF), Naive Bayes (NB), Support Vector Machine (SVM), Artificial Neural Network (ANN) and K-Nearest Neighbor Algorithm (kNN) are compared and experimented with immunotherapy and cryotherapy datasets. To expand the range of performance characteristics, feature selection techniques of the unbalance classes and reduction of dimensionality are implemented. Analysis of multiple algorithms shows that Random Forest (RF) outperformed others, achieving 95% accuracy, 88% sensitivity and 98% specificity. Khatri et al., (2018) [10] used the 10-fold cross-validation technique of J48. In the study, genetically programmed traits are created with original traits. J48 and J48 + GA are implemented; as a result, the classification results improved from 82.22% to 96.66% for the immunotherapy dataset and from 93.33% to 98.88% for the cryotherapy dataset. The study concluded that the research work could be further extended by applying genetic trait construction with various ensemble learning algorithms.

3) Usage of Ensemble Algorithms: Putra et al., (2018) [41] recommended that it is challenging for researchers to choose an appropriate wart treatment through machine learning. The expectation is to compare cryotherapy and immunotherapy treatments and methods to choose the best treatment. The study aims to improve accuracy using AdaBoost and Random Forest machine learning algorithms. An accuracy of 96.6% in cryotherapy treatments and 91.1% in immunotherapy treatments is achieved by implementing 10-fold cross-validation.

Putra et al., (2018) used in another study AdaBoost with random forest and classification and regression trees (CART) for cryotherapy and immunotherapy treatment methods.

4) Utilisation of Other Algorithms: Khozeimeh et al., (2017) [8] deployed a rules-based fuzzy logic algorithm that uses a network-based adaptive fuzzy inference system to account for the performance of cryotherapy and immunotherapy treatments. The classification performance of the applied method resulted in an accuracy of 80%, a specificity of 70%, and a sensitivity of 87%. Abdar et al., (2019) [43] applied an evolutionary diagnostic system (IAPSO-AIRS), 90% accuracy was achieved for the immunotherapy dataset and 96.4% for cryotherapy. The study investigated the therapeutic response in immunotherapy and cryotherapy. Immunotherapy and cryotherapy datasets are integrated into one dataset, consisting of 90 observations each, these are combined into 180 instances. Khozeimeh et al., (2017)suggest that the IAPSO AIRS system could be further optimised using deep learning.

C. Classification

To evaluate the classification performance of algorithms implementations, specificity, sensitivity and accuracy are calculated to determine the effectiveness of the applied algorithms. Equations 1, 2, and 3 demonstrate the formulas for specificity, sensitivity and accuracy:
TP = True Positive
TN = True Negative
FP = False Positive
FN = False Negative

$$\textbf{\textit{Accuracy}} = \frac{TP + TN}{FP + FN + TP + TN} \tag{1}$$

$$\textbf{\textit{Sensitivity}} = \frac{TP}{TP + FN} \tag{2}$$

$$\textbf{\textit{Specificity}} = \frac{TN}{TN + FP} \tag{3}$$

The research papers usually evaluate the classification performance in terms of accuracy, sensitivity and specificity, which are indicated in Tables VIII and IX, utilising immunotherapy or cryotherapy datasets as case studies. Nugroho et al., (2018) [44] attained an accuracy of 84.4% sensitivity of 91.4% and specificity of 55%. Meanwhile, Akyol et al., (2018) [45] obtained an accuracy of 89.3% sensitivity of 95.7% and specificity of 60%. The reason for variation in performance in terms of accuracy, sensitivity and specificity may be the variation in the configuration of the algorithms, the further optimisation of the methods and the selection of dissimilar features for classification.

TABLE VIII
VARIOUS RESEARCH PAPERS' CLASSIFICATION OUTCOMES REGARDING IMMUNOTHERAPY DATASET

Classification of Immunotherapy Dataset			Related Research Literature
Accuracy	**Sensitivity**	**Specificity**	
94.6%	96%	89.5%	Rahman et al., (2020) [19]
83.3%	87%	71%	Khozeimeh et al., (2017) [8]
90%	97.2%	63.2%	Akben (2018) [5]
84.4%	91.4%	55%	Nugroho et al., (2018) [44]
88.1%	-	-	Jain et al., (2018) [46]
91.1%			Putra, Setiawan and Wibirama, (2018) [41]
84%	-	-	Basarslan et al., (2018) [47]
100%	100%	100%	Ghiasi and Zendehboudi, (2019) [42]
83.3%	-	-	Degirmencie al., (2018) [48]
89.3%	95.7%	60%	Akyol et al., (2018) [45]
88.6%	93%	86%	Guimarães et al., (2019) [9]
84.4%	-	-	Abdar et al., (2019) [43]
76.2%	-	-	Jia et al., (2019) [49]
80%	-	-	Uzun, Isler and Toksan, (2018) [50]

TABLE IX
PERFORMANCE COMPARISON OF RELATED RESEARCH LITERATURE CLASSIFYING CRYOTHERAPY DATASET

Classification of Cryotherapy Dataset			Related Research Literature
Accuracy	**Sensitivity**	**Specificity**	
95.9%	94.3%	97.4%	Rahman et al., (2020) [19]
80%	82%	77%	Khozeimeh et al., (2017) [8]
94.4%	89.6%	100%	Akben (2018) [5]
93.3%	88.5%	98%	Nugroho et al., (2018) [44]
94.8%	-	-	Jain et al., (2018) [46]
96.6%	-	-	Putra et al., (2018) [41]
95.4%	-	-	Basarslan et al., (2018) [47]
100%	100%	100%	Ghiasi and Zendehboudi, (2019) [42]
93.1%	-	-	Degirmenci al., (2018) [48]
96.4%	94.4%	100%	Akyol et al., (2018) [45]
84.3%	97%	41%	Guimarães et al., (2019) [9]
94.4%	-	-	Abdar et al., (2019) [43]
80%	-	-	Uzun, Isler and Toksan, (2018) [50]

V. SOFTWARE TOOLS

Data analysis tools are used to analyse the datasets, such as Weka and Python. Weka and Python have some advantages and disadvantages in terms of reading and analysing the data; however, using both tools together can lead to an optimal solution by getting the most out of each tool and overcoming technical hurdles such as reading the immunotherapy dataset. Weka can read data in CSV and ARFF (Attribute-Relation File Format) formats. In Weka data analysis has been expanded to include additional features, such as histogram and scatter matrix. Weka is an academic data mining tool that comes with data analysis and machine learning capabilities as it is both simple and comprehensive. The weka analysis tool is Java-based, open-source and includes provisions such as classification and data preprocessing. In numeric computing, another widely used software programming tool is Python: it contains several useful packages and libraries for algorithm implementation and data analysis, including classification and data visualisations [51]. The outstanding Python libraries for analysing and visualising data are Matplotlib, Seaborn, Pandas, and Plotly. A beneficial implementation of various machine learning algorithms can be found in the Scikit-learn package, for example, Random Forest and *k*-NN among others [52].

VI. GAPS IN LITERATURE

Several research papers mentioned related work in the literature of published research, the focus was on predicting the treatments utilising machine learning algorithms in terms of accuracy, sensitivity and specificity, for example, Rahman et al., (2020) [19]; Akben (2018) [5] and Nugroho et al., (2018) [44]. Few studies have forgotten to mention the most important parameters of sensitivity and specificity, such as Jain et al., (2018) [46]; Basarslan and Kayaalp, (2018) [47]; Degirmencie al. (2018) [48] and Abdar et al., (2019) [43]. The immunotherapy dataset is unbalanced, mentioning sensitivity and specificity is essential because only the accuracy is not sufficient in this case. The expert prediction system and associated machine learning prediction rules should be optimised: therefore, all studies optimised the performance because the more accurate the prediction, the more patients can be treated accurately [5]. In addition, health professionals have difficulty understanding the results of research due to the lack of some details; for example, the code and tools used are not mentioned in Guimarães et al., (2019) [9].

Akben, (2018) [5] converted the results of the classification into images. The classification prediction is presented as an image and visualised as a function of the time elapsed since the disease was present and the age of the patient. The challenge of the unbalanced immunotherapy dataset is neglected in Akben, (2018) [5], focusing on the unbalance data may further improve classification outcomes. Akben, (2018) [5] did not cite related research literature. Meanwhile, CÜvitoğlu and Işik (2018) [18] provided related work from only one research article, which is not sufficient for the status of the current research. Related research literature has been discussed in many research articles, Rahman et al., (2020) [19] mentioned only one related research article and Akben (2018) [5] should have mentioned the related research literature in a separate section. Several research papers also used the cryotherapy dataset; see Table IX. Ghiasi and Zendehboudi (2019) [42] outperformed the others and achieved 100% accuracy, sensitivity and sensitivity for the classification of both immunotherapy and cryotherapy datasets.

A. Addressing Selected Research Papers

This section describes four research papers selected from the research literature [CÜvitoğlu and Işik (2018) [18]; Rahman et al., (2020) [19]; Fazriansyah et al., (2020) [20]; and Akben, (2018) [5]. A common perspective of these selected research is that the research papers analysed both the immunotherapy and cryotherapy datasets; hence these are referred to as sister research papers.

1) Strong Points and Achievements: The main addressed research paper is CÜvitoğlu and Işik (2018) [18]. The reason for choosing (CÜvitoğlu and Işik, 2018) [18] instead of the sister research papers, as it is based on a better algorithms selection, simplicity, comprehensive formulation and good structure. CÜvitoğlu and Işik (2018) have a good organisation of the implemented algorithms, which makes these reproducible compared to Fazriansyah et al., (2020) [20] and Akben, (2018) [5], who did not provide enough information to be replicated. The strongest side of the addressed research paper in question is the selection of dissimilar algorithms, as many algorithms are selected from different categories, such as the nonlinear algorithm [k-Nearest Neighbors and Support Vector Machines (SVM)]. Applying different algorithms can improve the performance of the supervised classification. Fazriansyah et al., (2020) [20] used the neural network only; however, many important visualisations are demonstrated; these make the concepts easier to understand. Meanwhile, Rahman et al., (2020) [19] have many useful tables which are useful for comparing the performance of machine learning methods.

2) Disadvantages: CÜvitoğlu and Işik (2018) [18] did not include the configuration of the implemented algorithms and the tools used are not mentioned, without this essential information, it will be difficult to reproduce the results, although CÜvitoğlu and Işik (2018) [18] is an excellent research paper, as described in the previous section.

VII. GAPS IN APPLICATIONS

Some research papers on immunotherapy in warts did not focus on the unbalanced issues thoroughly. Furthermore, health professionals have difficulty understanding research because some details are missing. In addition, the researcher did not usually combine various software tools by taking the best out of each. The published research is normally challenging in terms of reproduction.

VIII. REPRODUCING ALGORITHMS' IMPLEMENTATIONS

In this study, algorithms developed in medical and health-related research papers are reproduced. Bayes Network, J48 (C4.8 decision trees based), *k*NN, ZeroR, Serialised Classifier, Multi Scheme, Artificial Neural Network and Random Forest are implemented to classify datasets of immunotherapy [17], diabetes [21], cryotherapy [22], exasens data [23] and "one unbalanced dataset" [24]. However, this section demonstrates the classification results of immunotherapy data only. Based on the classification, the four better-performing algorithms are indicated in Table X.

TABLE X
COMPARISON OF CLASSIFICATION RESULTS OF RANDOM FOREST, *k*NN, J48, AND ARTIFICIAL NEURAL NETWORK ALGORITHMS IMPLEMENTATIONS

Algorithm	**Performance**
Random Forest	1
k-Nearest Neighbours algorithm	2
J48	3
Artificial Neural Network	4

The Random Forest algorithm and *k*-Nearest Neighbours algorithm outperformed the others, in this study, therefore these are compared with published research publications namely, Rahman et al., (2020) as well as CÜvitoğlu and Işik, (2018).

A. Comparison of Results with Publications

Table XI demonstrates the outcomes of *k*-Nearest Neighbours algorithm and Random Forest implementations, classifying the immunotherapy dataset. Accuracy of 88.88%, specificity of 60% and sensitivity of 95.45% are obtained by Random Forest, 30% for testing and 70% for training. The reason for the difference in classification of this study, Rahman et al., (2020) [19] and CÜvitoğlu and Işik, (2018) [18] is because Rahman et al., (2020) have further optimised *k*-Nearest Neighbours algorithm and Random Forest implementations, meanwhile CÜvitoğlu and Işik, (2018) [18] used all attributes of the dataset as input without any feature selection. The results obtained in this study are more suitable when compared with CÜvitoğlu and Işik, (2018), because when implementing *k*-Nearest Neighbours algorithm and Random Forest all attributes are utilised as CÜvitoğlu and Işik, (2018). Comparing the accuracy, sensitivity and specificity of *k*-Nearest Neighbours algorithm and Random Forest implementations with the research literature in Table XI, illustrating the classification of the immunotherapy dataset using Weka and Python.

TABLE XI
RANDOM FOREST AND *k*NN IMPLEMENTATIONS' OF THIS STUDY COMPARED WITH RELEVANT ACADEMIC PUBLICATIONS

Algorithm	Accuracy	Specificity	Sensitivity
Random Forest			
10-fold cross validation	81.11%	58.33%	84.61%
Weka Trian-Test Sets	88.88%	60%	95.45%
Python Trian-Test Sets	88.88%	-	-
Rahman et al., (2020) [19]	92.7%	84.8%	95.1%
CÜvitoğlu and Işik, (2018) [18]	88%	50%	99%
k-Nearest Neighbours Algorithm			
10-fold cross validation	72.22%	33.33%	81.94%
Weka Trian-Test Sets	70.37%	25%	89.95%
Python Trian-Test Sets	77.77%	-	-
Rahman et al., (2020) [19]	80.9%	93.6%	78.1%
CÜvitoğlu and Işik, (2018) [18]	61%	10%	74%

To achieve good results as Rahman et al., (2020) [19] or better, advanced techniques are applied such as balancing the classes of the immunotherapy dataset, and the results are compared with research literature again, specifically with Rahman et al., (2020) [19] and Akben, (2018) [5] aiming to find the best versions of *k*-Nearest Neighbours algorithm and Random Forest. Table XII compares the accuracy, sensitivity and specificity of the implemented algorithms *k*-Nearest Neighbours algorithm (*k*NN) and Random Forest with Rahman et al., (2020) [19] and Akben, (2018) [5]. Rahman et al., (2020) [19] excels in outstanding accuracy and specificity, however, Akben, (2018) achieved better sensitivity.

TABLE XII
ILLUSTRATING ACCURACY, SENSITIVITY AND SPECIFICITY OBTAINED IN THIS STUDY WITH RAHMAN ET AL., (2020) [19] AND AKBEN, (2018) [5]

Study	Accuracy	Specificity	Sensitivity
Rahman et al., (2020) [19]	94.6%	89.5%	96%
Akben, (2018) [5]	90%	63.2%	97.2%
This study	97.36%	93.76%	100%

IX. DISCUSSION

The datasets of immunotherapy [17], diabetes [21], cryotherapy [22], exasens data [23], B-cell data [36] and sample serum [37] are selected based on that these are related to health and immunotherapy. The classification algorithms used on the datasets may be generalised to other health domains. This will be useful for health professionals and researchers when deciding to study and implement the algorithms on other datasets unmentioned in this study. However, other datasets may have specific aspects which should be considered before applying the tools and algorithms. Combining similar datasets may reveal better results in terms of classification, as some datasets are small.

The immunotherapy dataset contained many irrelevant attributes; additionally, it was a challenge to analyse the dataset with only a few crucial attributes for productive data analysis and better performance. During the practical work, some obstacles were faced when analysing the datasets. It took a great deal of time to convert the file to ARFF (Attribute-Relation File Format). The challenge was to understand that Weka exclusively read a dataset in a specific file format such as CSV. Weka contains a function that converts the input file to the respective readable format.

Weka and Python are used by researchers for data analysis and algorithm implementation. However, the challenge was to consider whether Python or Weka was preferable when performing various tasks. The optimal solution was found by utilising both tools, which provided an opportunity to make comparisons. Identifying the type of attributes solved this issue. Many studies used only one data analysis tool either Python or Weka, several tools are not combined for data analysis and algorithms implementations, and this is a gap in the application. Every software tool has some advantages and disadvantages. A combination of various software tools, for example, Weka and Python, may reveal better classification. The software tools could be supplemented, to achieve meaningful results in different domains, by taking the best out of each.

Many immunotherapy domains are indicated covering many aspects, to allow the researcher to study a specific topic of interest. In addition, several related fields are presented to be inclusive. Facilitating the relevant choices with the possibility to be selective as well.

Gaps in published literature are that some research papers, Jain et al., (2018) [46]; Basarslan and Kayaalp, (2018) [47]; Degirmencie al. (2018) [48] and Abdar et al., (2019) [43] neglected to mention the most important parameters of sensitivity and specificity. The immunotherapy dataset is unbalanced, therefore, when evaluating the classification, sensitivity and specificity are essential because only accuracy is not sufficient in this case. Many studies did not focus on the unbalanced issues thoroughly. In addition, some gaps are found when the algorithms used by researchers are reproduced. The published research is normally challenging in terms of reproduction. Furthermore, health professionals have difficulty understanding research as some details are missing; For example, the code and tools used are not mentioned by Guimarães et al., (2019) [9]. In addition, during algorithm implementations, finding the target feature to classify the treatments was an obstacle.

When considering which experiments can be important to undertake in further research, considering the algorithms and software tools used by other studies are explored, to find what should be analysed in-depth. Algorithms or classifiers are organised as non-linear, a combination of linear and non-linear, ensemble methods as well as other algorithms.

X. CONCLUSION

First, a critical review of the published research in immunotherapy is performed to be updated on the current research and find some gaps in the literature. Second, some algorithms implemented in research papers are reproduced, to consider the application gaps as well, further research is regarding addressing the gaps.

Digital resources of immunotherapy are explored, acquiring small and challenging unbalanced datasets immunotherapy [17], diabetes [21], cryotherapy [22], exasens data [23], B-cell data [36] and sample serum [37]. However, the data is limited and therefore needed to be supplemented with other health-related datasets. Various research papers explored both datasets together as well. Four research papers [CÜvitoğlu and Işik (2018); Rahman et al., (2020) [19]; Fazriansyah et al., (2020) [20]; and Akben, (2018) [5]] are particularly addressed, and the critical review revealed that more research is needed to address the unbalanced immunotherapy datasets.

Random Forest and *k*-Nearest Neighbours algorithm implementations in published literature are reproduced in this study, classifying the immunotherapy dataset. Random Forest performed better obtaining an accuracy of 88.88%, specificity of 60% and sensitivity of 95.45%, 30% for testing and 70% for training. Accuracy of 92.7% specificity of 84.8% and sensitivity of 95.1% are attained by Rahman et al., (2020), and the classification results are better than CÜvitoğlu and Işik, (2018). To consider the differences in the classification of this study, Rahman et al., (2020) [19] and CÜvitoğlu and Işik, (2018) [18], *k*-Nearest Neighbours algorithm and Random Forest implementations are further optimised by Rahman et al., (2020) [19]. Meanwhile, all attributes of the dataset are used as input without any feature selection by CÜvitoğlu and Işik, (2018) [18]. The classification results obtained in this study are more suitable to be compared with CÜvitoğlu and Işik, (2018), implementing *k*-Nearest Neighbours algorithm and Random Forest all attributes are utilised as CÜvitoğlu and Işik, (2018).

Several research papers contributed to the analysis of immunotherapy datasets by developing various machine learning algorithms and methods to classify and analyse the datasets. For example, Uzun, Isler and Toksan, (2018) [50] utilised *k*-Nearest Neighbours algorithm (*k*NN). Rahman et al., (2020) [19] and others implemented Random Forest. In the case of unbalanced datasets, the studies either modified the algorithms or used filters and data preprocessing before algorithm implementation to enhance the classification results.

A. Recommendations for Further Research

Further research could be to conduct experiments addressing the gaps in research publications and applications, as some publications are difficult to understand for health professionals. A need for under-stable multidisciplinary research exists filling the gap between theory and application by focusing on practical solutions. An alternative method is needed to analyse the imbalanced immunotherapy datasets. Experiments are suggested for the classification of the unbalance challenges effectively and simply using the 'more is less' principle, focusing on efficiency, implementing a new algorithm or modification of an existing one or a combination of these.

The plan regarding further research is summarised in the following: Continuing studying immunotherapy-related research papers from published literature. Designing and conducting more experiments on the data with a data-driven perspective. Finding alternative solutions for analysing immunotherapy data by addressing small unbalanced data challenges.

The backbone of the upcoming research will be researching slow and steady finding the answers to the questions. Both the literature review and the results of the experiments show that an innovative method for analysing the unbalanced immunotherapy dataset can be useful as existing models are not so effective. Next, further research aims to improve current algorithms or to discover a new method or a combination thereof. Further research will contribute by being a necessary bridge, filling the gap of understanding between computer scientists, software developers and health professionals, making the diagnosis of immunotherapy treatments understandable.

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