Detecting factors associated with polypharmacy in general practitioners’ prescriptions: A data mining approach

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Abstract

Prescribing and consuming drugs more than necessary is considered as polypharmacy, which is both wasteful and harmful. The purpose of this paper is to establish an innovative data mining framework for analyzing physicians’ prescriptions regarding polypharmacy. The approach consists of three main steps: pre-modeling, modeling, and post-modeling. In the first step, after collecting and cleaning the raw data, several novel physicians’ features are extracted. In the modeling step, two popular decision trees, i.e., C4.5 and Classification and Regression Tree (CART), are applied to generate a set of If-Then rules in a tree-shaped structure to detect and describe physicians’ features associated with polypharmacy. In a novel approach, the response surface method (RSM) as a tool for hyper-parameter tuning is simultaneously applied along with correlation-based feature selection (CFS) to enhance the performance of the algorithms. In the post-modeling step, the discovered knowledge is visualized to make the results more perceptible, then is presented to domain experts to evaluate whether they make sense or not. The framework has been applied to a real-world dataset of prescriptions. The results have been confirmed by the experts, which demonstrates the capabilities of the data mining framework in the detection and analysis of polypharmacy. The derived If-Then rules can be beneficial for healthcare managers and policy-makers to recognize physicians’ prescribing pattern and take suitable action to support medicines management and develop high quality prescribing guidelines.

Keywords: decision tree, CART, C4.5, parameter tuning, response surface method (RSM), rational use of drugs

1. Introduction

Pharmaceutical spending is a major portion of total healthcare costs. This proportion differs significantly among countries based on their income; pharmaceutical expenditure as a share of total health cost varies from 19.7% in the high-income economies to a mean of 30.4% in low-income ones [1]. World Health Organization (WHO) has informed that about 50% of all drugs are unsuitably prescribed, dispensed, or sold [2]. Irrational use of drugs remains an extremely severe
and widespread issue across the world, especially in developing countries [3]. It is both wasteful and harmful [4]. Despite it is a global problem, few countries are monitoring medicines prescribing and making sufficient policy and taking appropriate action to cure the situation [5]. The essential steps for limiting the irrational use of drugs consist of recognizing the types, extent, and causes for their irrational prescribing and consumption [6]. WHO and the International Network of Rational Use of Drugs (INRUD) have introduced a group of medicine prescribing indicators as measures to prescribe quality evaluation [7]. The first indicator, the average number of drugs prescribed per encounter, is used to measure the extent of polypharmacy. Polypharmacy is in association with unnecessary and/or inappropriate drug prescribing [8]. It does not matter whether the patient has taken them or not [9]. Although various numerical cut-offs have been used to describe polypharmacy, the usual definition is the recommendation of two or three drugs per prescription [9].

“It is very challenging to reach a conclusion about polypharmacy and its related factors because of the wide variety in the definitions applied” [10]. Physicians, pharmacists, and patients are all involved as well as healthcare managers and policy-makers. In Australia [11] and [12], and Italy [13] tried to recognize patients’ attitudes, opinions, and experiences regarding polypharmacy and readiness to withdraw medications. Quinn and Shah analyzed the prevalence of polypharmacy in 4 billion patient-months of outpatient prescription drug claims between 2007 to 2014 in the united states [14]. According to [15], the factors possibly causing polypharmacy can be divided into four major categories: 1) Factors related to the healthcare system, including the development of society and healthcare services, development of new technologies and therapies, and increased use of drug therapy. 2) Factors related to patients, containing age, sex, ethnicity, socioeconomic status, behavior, clinical condition, and medical therapy. 3) Factors related to physicians, including physician practice environment, guidelines, behavior, and prescribing habits. 4) The interaction between doctor and patient. Bjerrum et al by analyzing prescription data written by Danish general practitioners (GPs), utilizing backward stepwise linear multiple regression, identified that the practice structure, workload, clinical work profile, and prescribing profile were the predictors of major polypharmacy (using ≥ 5 drugs concurrently). They also claimed that the occurrence of major polypharmacy was meaningfully lower for female GPs than for male GPs; however, the age of physicians or experience did not affect the major polypharmacy [16]. Anthierens et al. directed semi-structured interviews to study 65 Belgian GPs’ views and beliefs on polypharmacy to classify the role of the GPs in improving prescribing patterns [17]. In a study conducted by O’Dwyer et al., demographic variables and reported chronic health conditions were studied in association with polypharmacy in 734 Irish elderslies with intellectual disability using a multinomial logistic regression model [18]. Ie et al. explored factors associated with 61 family physicians’ prescribing behavior prescribed for 932 patients using multivariable regression. They considered patient-related characteristics including gender, age, race, health condition. They also investigated physician-related features consist of gender, age, years since graduation, position, and their responses to a survey about polypharmacy and potentially inappropriate medicines (PIM). They claimed that physicians who care more about the number of prescribed medications and use the Beers List recommended fewer drugs and PIMs; however, physicians related factors including gender, experience, and perceived confidence were not associated with prescribing behavior at family medicine residency practices [19]. The findings from a study by Slater et al. showed that patients related factors including lower wealth, increasing age, obesity, and the occurrence of chronic conditions are related to polypharmacy prevalence among patients older than 50 years in
primary care in England [20].

Furthermore, many studies all around the world, such as [21], [22], [23], [24], and [25], analyzed the average number of drugs prescribed per encounter as well as the other indicators of WHO and INRUD to identify the extent of rational use of drugs. On the other hand, Cerrito suggested using a data mining approach to examine the adverse effects caused by polypharmacy in cardiology patients [26]. Data mining is an attractive approach in the pharmacovigilance field of study to identify adverse drug events (ADE) and adverse drug reaction (ADR), which focused on post-marketing surveillance of medicines. For example, it can be mentioned researches conducted by [27], [28], [29], and [30].

Despite the theoretical development of data mining methods and their notable applications in various fields of healthcare studies in recent decades [31], to the best of the authors’ knowledge, a data mining approach has not been applied to analyze the rational use of drugs including polypharmacy. Meanwhile, a tremendous, amount of drug prescription data is continuously generated by physicians and stored in health information systems. Analysis of this kind of data will offer solutions to rationalize the use of drugs, and as a consequence it can improve the patients’ health condition and decrease insurance costs. Therefore, the question that arises is whether data mining can be used in the analysis of prescription quality and rational use of drugs. Also, whether an organized and usable data mining framework can be provided for the analysis of huge prescription data to understand the extend of polypharmacy. To answer the questions, the authors have developed an unprecedented data mining framework and have applied it to a real-world prescription dataset prescribed by GPs. In other words, in this paper, a data mining approach has been introduced. Then, to study its performance, the GPs’ prescribing pattern is monitored and analyzed regarding the average number of drugs recommended per prescription to appraise the extent of polypharmacy. Furthermore, the significant physician-related characteristics that are associated with polypharmacy are identified. It is necessary to mention, the choice of GPs is due to the fact that the majority of patients refer to them, consequently they should be involved in any prescription quality improvement practices [32].

The structure of the rest of the paper is as follows. Section 2 introduces a data mining framework for analyzing physicians’ prescribing patterns concerning polypharmacy. The next section shows how the proposed method is applied to a real-world prescription dataset. Section 4 contains results and discussion. Finally, the conclusion and outlines of the future works are presented in Section 5.

2. Data mining Methodology

The data mining framework applied in this paper is inspired by ASUM-MD [33]. As it is shown in Fig. 1, it is carried out in three main steps: pre-modeling, modeling, and post-modeling. Real-world data is mostly of poor quality, and also it often not in the desired format for the use in the data mining algorithms. Consequently, the use of it in the machine learning algorithms can lead to misleading results. So, before taking any action, it is necessary to evaluate the data and fix its potential deficiencies and shortcomings. It is especially important for healthcare databases that contain patients, physicians, and their prescriptions records. Identification, collection, preparation, and improvement of the data are made in the pre-modeling phase. Then, in the modeling step, the appropriate machine learning algorithms are applied for diagnosing polypharmacy and identifying the physician-related characteristics associated with it. Because the results of the modeling phase are usually incomprehensible, it is necessary to present them in a more understandable format to the domain experts. Then, their opinions on the approval or rejection of the discovered patterns

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should be obtained, and their feedback should be applied in different previous stages to achieve better results. This is done in the post-modeling phase. Further details on the data mining framework are provided as follows.

2.1. Pre-modeling

3.1.1. Data gathering and understanding

The required raw data should be collected from trusted sources regarding research objectives and business level requirements. Also, the data may be described using visualization techniques and tools. Patient, physician, and prescription data is required to be collected in the study.

3.2.1. Data preparation

In the data preparation task, the quality of the raw data is evaluated and improved. It aims to get rid of irrelevant, noisy, and inconsistent data from the raw data. This phase also consists of feature extraction, data transformation, as well as handling missing values. Also, this phase includes data compression and data reduction. Because different data sources, i.e., patient data, prescription data, physician data, and some supplementary data are used, it is necessary to integrate them carefully. At the end of this step, the prepared data is ready to be mined.

2.2. Modeling

In the modeling step, appropriate machine learning algorithms and data mining techniques are applied based on the business goals and the quality of the prepared data. The prepared dataset is split into training and testing subsets based on a predetermined strategy. The training dataset is used to build a model and tune its parameters, whereas the testing dataset is utilized for performance evaluation of the model. In the study, a holdout dataset approach is used, and the division is made up to assign 50% to the training and 50% to the testing subsets using the random stratified sampling strategy. Therefore, the proportion of the two different classes (0 or 1 for polypharmacy) in the primary dataset remains the same in both training and testing datasets.

3.2.1. Model building

In this sub-step, the modeling tool and machine learning algorithms are run on the training dataset to build one or more models. Also, it is essential to tune the parameters of each applied algorithms to the appropriate values. Although feature selection is a part of data preparation, it may have interaction with parameter tuning. Therefore, they are simultaneously applied to consider their possible interaction in the model building sub-step. Since each machine learning algorithm needs particular data requirements, it sometimes is necessary to return to the data preparation phase and make the necessary changes to satisfy the desirable requirements.

In the research, the main problem is polypharmacy detection, which is a classification problem. The decision trees are a common and popular way of classification because of their accuracy, simplicity, ease of use and interpretation [34]. Decision trees build a model demonstrated by a group of If-then rules in a tree-shaped structure. So, decision tree classifiers are applied to recognize polypharmacy and describe the factors associated with it.

3.2.2. Model evaluating
To ensure the effectiveness of the generated models, it is necessary to assess their performance regarding the evaluation criteria such as accuracy. Testing dataset and the 10-fold cross-validation method is employed to evaluate each algorithm’s performance. The authors assess each algorithm individually as well as compare them with each other. Also, the transparency and comprehensiveness of each model is evaluated.

2.3. Post-modeling
Finally, the sophisticated results of the modeling phase are presented to domain experts in an understandable format. Their opinions on the discovered patterns are obtained, and their feedbacks are applied to achieve more rational results.

3.3.1. Visualization
Visualization is the practice of communicating and displaying extracted pattern and discovered knowledge in a way that can be easily understood, analyzed and remembered. Employing various graphical or visual formats such as charts, graphs, and statistical representation is common in visualization. In this study, the discovered patterns are visualized in the form of tree.

3.3.3. Results evaluation
The data mining results should be interpreted in terms of the application and the original business objectives. With the aid of the domain experts, it is necessary to review the discovered knowledge to see whether it makes logical sense and is useful for the end users. The feedback can be applied to improve the data mining process and achieve more rational outcomes.

3. Detecting polypharmacy in general practitioner’s prescriptions
In this section, the developed data mining framework is used to identify polypharmacy and detect factors associated with it. For this purpose, a real-world database is used which contains the prescription data of general practitioners (GPs).

3.1. Pre-modeling

4.1.1. Data gathering and understanding
The raw data which is used in this research has been received from the National Center for Health Insurance Research of the Iran Health Insurance Organization in the format of MS SQL Server 2012. The raw dataset includes patient's insurance code, patient's insurance fund, patient's birthday, patient's sex, the province where the patient's insurance booklet is issued, prescription code, pharmacy code, physician's medical council number, visit date, prescription dispense date, prescription fee, Health Insurance Organization’s share of the prescription fee, as well as the details of the drugs available in each prescription including drug code, amount, and fee.

In the study, only physicians were considered who have averagely prescribed at least 24 prescriptions per year. In summary, the raw dataset consists of 3,860,835 prescriptions and 13,887,444 medicines. They were prescribed by 9,552 GPs for 1,962,417 different outpatients. The prescriptions were dispensed by 2,213 pharmacies in Tehran province between 21 March 2015 and 20 March 2016 and reimbursed by Iran Health Insurance. The average and the standard deviation of the number of drugs per prescription is 3.16 and 0.85, respectively.
4.1.2. Data preparation

In this research, the quality of the initial data has been carefully assessed. The data which was not in the appropriate format was identified and attempted to find the right estimation of them; otherwise, they were expelled from the dataset. While GP’s medical council number, patients’ insurance code, and drug identification code has a standard format, they did not have this predefined format in some record. For example, while the medicines were recorded as a five-digit number in the Health Insurance database, some of the them logged as a three-digit number, which was invalid. Also, the records which include missing values have been identified and isolated.

To complete the initial dataset, it was attempted to collect additional data about physicians, including the gender, age, experience, the place of study, and the place of work. However, the data was not available to the research group. So, to enrich the dataset, some novel features are extracted from existing ones. In fact, the new features were not directly available in the prescription database. However, they were calculated by authors using SQL codes considering the factors leading to polypharmacy mentioned in the literature or by approval of the domain experts. For example, in the initial database, it is only specified which doctor prescribed for which patient. However, the total number of patients who have referred to a certain physician has been extracted by using SQL, and added to the physician’s profile. The feature determines the work burden of the GP. All extracted features are briefly presented as follows.

Gender: The gender of physicians was not declared in the dataset. However, the doctor’s name is extracted by matching the medical council number with another supplementary dataset. Next the gender was specified and added to the dataset by using a database of people’s first names.

Experience: Given the fact that the medical council number assigned to each physician is an ordinal number starting from number one, it can be claimed that a physician with a smaller medical council number is more experienced. To create a feature that represents experience, the medical council number has been discretized at intervals of 40,000 units. By doing this, all physicians are divided into four separate categories 1 to 4. Group 1 identifies the most experienced, while group 4 identifies the least experienced.

Drug Diversity (DD): The number of different drugs prescribed by each GP is calculated. It may represent the range of drugs that each GP is interested to prescribe.

Average cost of prescriptions (ACPr): The average cost of prescriptions for each GP.

Total number of patients (TNPa): Given the fact it is clear that each GP prescribes for whom, the total number of patients referred to each GP is calculated.

Percentage of female patients (PFPa): The percentage of female patients of each GP.

Percentage of male patients (PMPa): The percentage of male patients of each GP.

Percentage of resident patients (PRPa): The percentage of the patients who their insurance booklets issued inside of the studied region (Tehran province) is calculated for each GP.

Percentage of non-resident patients (PNRPa): The percentage of the patients who their insurance booklets issued outside of the Tehran province is computed for every GP.

Percentage of special patients (PSPa): The percentage of patients with a special disease such as Thalassemia.

Percentage of ordinary patients (POPa): The percentage of patients who have not special conditions.

Percentage of patients in age group i (PPaAGi): WHO uses the following age groups for estimation of the global burden of disease [35]: neonatal (<28 days), 1-59 months, 5-14, 15-
29, 30-49, 50-69, 70 years and older. However, in the study, due to the data conditions, the age is considered for the following age groups: 5 years and younger (AG1), 5-14 (AG2), 15-29 (AG3), 30-49 (AG4), 50-69 (AG5), 70-94 (AG6). The percentages of patients in these age groups have been calculated for each GP.

**Percentage of patients in the i-th insurance fund (PPaFi):** There are four main insurance found: Employers (F1), Workers (F2), Rural (F3), and the other categories (F4). The percentages of patients in different insurance funds have been computed for each GP.

**Total number of prescriptions (TNPr):** The feature shows the total number of prescriptions which is prescribed by each GP.

**Average number of prescriptions per patient (ANPP):** The feature represents the average number of prescriptions which is prescribed by the GP for all of his/her patients. In other words, it illustrates the average number of referrals of each patient to the specific GP.

**Total number of pharmacies (TNPh):** The feature shows how many pharmacies have dispensed each GP’s prescriptions.

**Average number of prescriptions per pharmacy (APrPh):** The feature shows that, on average, how many prescriptions of each GP are dispensed in the affiliated pharmacies.

**Polypharmacy:** The feature demonstrates the class variable, which is binary. For each GP, if the average number of prescribed drugs per prescription is less than 3, then polypharmacy is zero; otherwise, it will be 1. Out of the 9,552 GPs, 5,252 instances were labeled as 1.

According to domain experts, the two variables, i.e. drug diversity and the average cost of prescriptions, may have a strong relationship with polypharmacy. In other words, the expensive prescription probably contains more drugs. Also, a physician who has more drug diversity may have prescribed more drugs per encounter. Therefore, in the following, these two features were discarded. It is necessary to mention that several features contain unknown and missing values. For example, the gender of some patients is unknown, or the age of them is null or invalid. In this case, the patient is considered for calculating the total number of patients; however, it is ignored in the calculation of gender or age group percentage. Also, the GPs whose patients’ data, i.e., gender, age group, and insurance fund, contained more than 10% of the missing values, were discarded. Since residency and specialty of patients contain considerable missing values, their related features have been ignored too. Given these conditions, the prepared dataset contains 5593 GPs, of whom 3295 had an average of more than three drugs per prescription. Table 1 represents details on the features applied in the modeling step.

### 3.2. Modeling

#### 4.2.1. Model building

In the study, the core problem is the detection of polypharmacy, which is a binary classification. So, C4.5 and CART (Classification and Regression Tree) are selected based on their performance and applicability in binary classification. Wu et al. have claimed that C4.5 and CART are among the top 10 useful and widespread data mining algorithms [36]. Also, they can generate a set of If-then rules in a tree-shaped structure, which can describe the physician-related factors associated with polypharmacy. It is necessary to mention some efficient methods such as support vector machines (SVMs), neural networks (NNs), and ensemble methods are not applied in the study, since they are black box data mining.
algorithms and do not provide interpretable and explainable results [37]. In other words, although they may have appropriate performance, their internal logic is hidden to users and cannot describe the factors associated with polypharmacy.

C4.5 is an evolution and extension of ID3 (Iterative Dichotomiser 3) developed by Quinlan[38]. It is probably the most widely used machine learning algorithm in practice to date [39]. This supervised classification algorithm can handle continuous data, missing values, noisy data, and generate rules from trees. C4.5 utilizes gain rate as the goodness of a split to choose an attribute for splitting the dataset. The classifier decides the best numerical split point which has the least misclassification error. Then splitting procedure is applied to the training dataset to generate the sub-nodes. Finally, the algorithm applies a pruning step to simplify the classification rules without any loss of accuracy [38]. The post-pruning process in C4.5 is grounded on weak statistical assumptions. However, it is extremely agile and, therefore, common in practice [39]. The algorithm has been used extensively in recent health studies [40], [41], [42], [43], [44].

CART was developed by Leo Breiman in the early 1980s. The algorithm, as its name implies, can produce both classification and regression trees. It generates binary trees. More specifically, by applying CART, the dataset is divided into the two subsets that their difference is the most based on the Gini index. It uses the cost-complexity pruning method, which is a post-pruning approach [39]. The CART classifier has the option of producing multivariate tests, i.e., the algorithm can use a linear combination of attributes in splitting procedure [34]. It also can handle the missing values. CART is a popular machine learning algorithm in the field of healthcare and medical research for more than two decades and has been utilized in various medical researches [42], [45], [46], [47], [48], [49].

To apply C4.5 and CART algorithms, J48 and SimpleCart were employed from the classify tab of the Explorer interface of WEKA (8.3.2). J48 is an open-source java reimplementation of C4.5 revision 8, the last non-commercial version of C4.5 [39]. SimpleCart is also the implementation of CART in WEKA. C4.5 and CART, like many other machine learning algorithms, contain a set of hyper-parameters that can affect their performance significantly. So, their values must be set carefully. Table 2 provides concise information about hyper-parameters that will be considered and tuned.

There are several methods for parameter tuning, including grid search, random search, Gaussian process, Bayesian optimization, and DOE based method. Recently, Lujan-Moreno et al. proposed a method for parameter tuning using DOE and response surface method (RSM) [50]. In this method, interaction among factors (parameters) is carefully considered; however, it is often ignored in hyper-parameter optimization studies [50]. RSM develops a response surface by creating regression models to characterize the dependence of performance of the applied algorithm on parameter configuration. Since formerly the shape of the response surface is indistinct, it is necessary to find a polynomial model that fits the relationship between the predictors and the response. A low-order model such as first and second-order polynomial models is often appropriate to illustrate such a relationship [51]. The second-order or “quadratic” polynomial model is usually favored as it delivers the best tradeoff between the modeling accuracy and computational effort and provides perfect response surface curvature around intended regions. The second-order RSM can be defined as [52]:
\[ y = \beta_0 + \sum_{j=1}^{k} \beta_j x_j + \sum_{j=1}^{k} \beta_j^2 x_j^2 + \sum_{i,j}^{k} \beta_{ij} x_i x_j + \epsilon \]  \hspace{1cm} (1)

RSM is a sequential method that, at each step, it moves in the direction of improvement for optimizing its objective. Since RSM creates a surrogate model, it can obtain valuable results with only limited experiments.

The central composite design (CCD) is one of the most prevalent RSM designs. As a rotatable design, it can be considered a factorial design in combination with some additional points, i.e., center point, and star points. They expand the cuboidal region of the initial factorial design. Across each factor level, the curvature of the response surface can be estimated by the additional points. Fig. 2 depicts a CCD for two continuous factors with two levels, where -1 and +1 show lower and upper level, respectively. Also, 0 demonstrates central point, and star points is created by \( \alpha \) [51].

Sometimes, it is necessary to optimize multiple objectives (responses) simultaneously. The desirability function is one of the most extensively applied approaches for optimizing multiple responses [52]. Each response \( R \) is transformed into an individual desirability function \( d \) ranging from 0 to 1, where 1 is the most desirable. If response \( R \) is considered to have a maximum value of objective or target \( T \),

\[
\begin{align*}
    d &= \begin{cases} 
        0 & y < L \\
        \left( \frac{y - L}{T - L} \right)^{t} & L \leq y \leq T \\
        1 & y > L 
    \end{cases} \\
\end{align*}
\]  \hspace{1cm} (2)

If the objective or the target of the response is to be minimized

\[
\begin{align*}
    d &= \begin{cases} 
        1 & y < T \\
        \left( \frac{U - y}{U - T} \right)^{t} & T \leq y \leq U \\
        0 & y > U 
    \end{cases} \\
\end{align*}
\]  \hspace{1cm} (3)

Setting \( t=1 \), the desirability function is linear. Setting \( t>1 \) results in a greater emphasis on getting close to the target value, and setting \( 0<t<1 \) makes this unimportant. If \( R \) is completely undesirable outside an acceptable region \( d_i=0 \), and if the response \( R \) has a completely desirable value at its goal or target, then \( d_i=1 \). The geometric mean of the individual desirability functions is an overall desirability function that should be maximized:

\[ D = (d_1 \times d_2 \times \ldots \times d_k)^{1/k} \]  \hspace{1cm} (4)

Where \( k \) denotes the number of responses.

On the other hand, since there are many features in the prepared dataset, it should also be decided whether to use feature selection techniques or not. Feature selection is productive in reducing dimensionality, taking away irrelevant and noisy data, simplifying models without much loss of the total information. In this work, Correlation-based Feature Selection (CFS) is utilized for feature selection. CFS is a fast algorithm, which makes it applicable for large datasets. It
evaluates the efficacy of individual features for predicting the class in the company of the level of inter-correlation among them using Eq. (5) [53].

\[ M_S = \frac{k \bar{r}_{fc}}{\sqrt{k + k(k - 1)\bar{r}_{ff}}}, \tag{5} \]

Where \( M_S \) is the score of a feature subset \( S \), including \( k \) features, \( \bar{r}_{fc} \) the average feature-class correlation, and \( \bar{r}_{ff} \) the average feature-feature correlation. If each member of a subset of features is extremely correlated with the class feature, while they are uncorrelated to each other, the subset receives a high score. CFS distinguishes irrelevant features as they are not correlated with the class. Also, it handles redundant attributes as they are highly correlated with one or more of the other features. However, CFS cannot recognize intense interaction among features since they are treated independently. It just identifies suitable features under moderate levels of interaction [53].

Applying RSM for parameter tuning makes it possible to consider the use of the feature selection method as a factor. It allows to decide whether or not to utilize the feature selection when the parameters of the algorithm are tuned. Since the novel approach uses the two methods simultaneously, the possible interaction between them can be distinguished.

4.2.2. Model evaluating

To prevent overfitting and evaluating the performance of each algorithm, it is necessary to re-apply C4.5 and CARD on a completely independent testing dataset. In order to achieve more accurate results, the 10-fold cross-validation method is employed. Also, each classifier is evaluated base on accuracy, sensitivity (or recall), specificity, precision, and F-measure using indicators from the confusion matrix displayed in Fig. 3 and the following mathematical equations according to [34] and [39].

\[ \text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN}, \tag{6} \]

\[ \text{Sensitivity (or Recall or true positive rate)} = \frac{TP}{TP + FN}, \tag{7} \]

\[ \text{Specificity (true negative rate)} = \frac{TN}{FP + TN}, \tag{8} \]

\[ \text{Precision} = \frac{TP}{TP + FP}, \tag{9} \]

\[ \text{F – measure} = \frac{2 \times \text{Recall} \times \text{Precision}}{\text{Recall} + \text{Precision}} = \frac{2 \times TP}{2 \times TP + FP + FN}, \tag{10} \]

Another metric for determining the quality of a data mining model is the receiver operating characteristic (ROC) curve. It is constructed by mapping the true positive rate (TPR), which is ‘sensitivity’ and the false positive rate (FPR), which is ‘1-specificity’. In the study, the area under the ROC curve (AUC) is used as a measure of the quality of the applied classifiers. The area closer to 1, the higher the quality of the classifier is [39]. Also, Size of Tree (SoT) is used to measure the simplicity and interpretability of the results. A smaller tree generated by a decision tree represents a simpler set of if-then rules. Also, the support and confidence are used as an
objective *interestingness* measures of extracted rules. Support of the rule $A \Rightarrow B$ is the percentage of transactions in a dataset in which the antecedent–consequent pair occur together (Eq. (11)). The rule’s confidence indicates the proportion of cases, including the consequent, among those comprising the antecedent, and thus it illustrates the rule’s reliability. (Eq. (12)) [34]. To calculate the support, the entire transactions in a dataset are counted, but if the total number of instances in a given class is considered, then another measure can be calculated as Eq. (13), which the authors have called *coverage*. In fact, it shows the power of a rule in recognizing a particular class.

$$\text{Support}(A \Rightarrow B) = P(A \cup B)$$  \hspace{1cm} (11)

$$\text{Confidence} (A \Rightarrow B) = P(A \mid B) = \frac{\text{Support}(A \cup B)}{\text{Support}(A)}$$ \hspace{1cm} (12)

$$\text{Coverage} (A \Rightarrow B) = P(A \cup B \mid C) = \frac{\text{Support}(A \cup B)}{\text{Support}(C)}$$  \hspace{1cm} (13)

The support–confidence framework cannot evaluate the real strength/lack of strength of the correlation between A and B. Therefore, alternative indicators such as *cosine* can be useful in detecting interesting data relationships. The cosine of A and B defined as Eq. (14), ranges from 0 to 1. The higher value of the measure demonstrates a stronger relationship between A and B [34].

$$\text{Cosine} (A \Rightarrow B) = \frac{P(A \cup B)}{\sqrt{P(A)*P(B)}} = \frac{\sqrt{P(A \mid B)*P(B \mid A)}}{\sqrt{\text{Support}(A)*\text{Support}(B)}}$$ \hspace{1cm} (14)

All classifiers are compared with each other based on the above-mentioned evaluation criteria.

3.3. **Post-modeling**

4.3.1 **Visualization**

To make the results and finding of this research clearer and more understandable for healthcare policy-makers and other end-users, C4.5 and CART performance metrics were pictured. Also, the discovered patterns were visualized in the form of a tree.

4.3.2 **Results Evaluation**

The extracted knowledge from the data mining framework was presented to the experts of the Iran Health Insurance Organization. Then their opinions on the discovered patterns and the generated rules for polypharmacy identification been received. Finally, the results have been modified based on their feedbacks.

4. **Results and Discussion**

The experimental results of applying the data mining framework on general practitioners’ prescriptions dataset are presented and discussed in this section. Recalling the parameters of the CART algorithm mentioned in Table 2, after some preliminary experiments, the region of the *minimum number of instances per leaf* (MNIL) has been considered between 1 and 49. To create appropriate CCD design, the low and high level of the parameter has been set to 8 and 42 respectively. Also, the low and high level of the parameter of the *percentage of training data used to construct the tree* (PTD) was adjusted to 0.312 and 0.882. Furthermore, 5 central points have been selected, and $\alpha$ is assigned the value of 1.414. Considering that using 1 SE rule to make
pruning decision (ISEr) was set to either false or true, and deciding on the use of CFS as the feature selection method was set to either yes or no, resulted in a CCD for RSM which required 52 runs of the CART in WEKA. The factors and corresponding responses, i.e., AUC and SoT were analyzed by RSM using Minitab software. The stepwise method with default setting was used to recognize a useful subset of predictors during each step. The results of the ANOVA analysis of AUC of CART algorithm demonstrates that the overall model is significant with $p<0.001$ and $R^2=0.83$, $R^2_{adj}=0.81$, and $R^2_{pred}=0.76$. The lack of fit test is not significant ($p=0.330$), which means the model has a good quality of fit. At the confidence level of 99.9%, all of the main factors other than FS is significant. However, FS is significant with $p<0.02$. On the other hand, only the quadratic term of PTD is statistically relevant at the confidence level of 99%. Also, its interaction with the MNIL is significant too. Similarly, the ANOVA of CCD for a total of 52 runs of SoT of CART shows the overall model is significant with $p<0.001$ and $R^2=0.68$, $R^2_{adj}=0.65$, and $R^2_{pred}=0.59$. Besides, the lack of fit test was not significant ($p=0.665$), which demonstrates the model goodness of fit. At the confidence level of 99.9%, just FS is not significant. Also, only the quadratic term of MNIL is significant. Furthermore, its interaction with ISEr is statistically significant. It can be concluded that the feature selection did not affect the tree size generated by CART. The optimum values of the parameters of CART were calculated to maximize AUC and minimize SoT using the desirability function approach. The optimum value of MNIL and PTD is 33 and 0.82 respectively; however, their default values are 2 and 1 respectively. The optimum value of ISEr is false, which is its default value. Besides, feature selection is recommended. The response surface plot of AUC and SoT demonstrates the curvature from second-order effects.

Similarly, the above steps were repeated for parameter tuning of the C4.5. Considering $\alpha=1.414$ the low and high level of MNIL has been considered 8 and 42, respectively to cover its region of interest, which is $[1,49]$. Also, the low and high levels of confidence factor (CF) were set to 0.074 and 0.426 respectively to cover its range of $(0,0.5)$. Furthermore, binary splits (BS) was set to either false or true, and deciding on the use of CFS was set to either yes or no. Considering 5 central points, a CCD for RSM, which entails 52 runs, was generated. ANOVA table of AUC of C4.5 depicts the overall model is significant with $p<0.001$ and $R^2=0.66$, $R^2_{adj}=0.61$, and $R^2_{pred}=0.46$ that indicates the model has a quite good quality of fit. The P-value of the lack of fit test cannot be calculated as the pure error is zero. Both MNIL and CF are statistically relevant, considering a significance level of 0.01. Meanwhile, just the quadratic term of MNIL is significant, with $p<0.001$. The fascinating finding is that there is an interaction between MNIL and FS with $p<0.001$, which demonstrates the hyper-parameter should be tuned along with the feature selection strategy because they have interaction. This issue is not recognizable in other popular methods of hyper-parameter tuning. The ANOVA table for RSM of SoT generated by C4.5 shows the overall model is significant, with $p<0.001$ and $R^2=0.72$, $R^2_{adj}=0.69$ and $R^2_{pred}=0.57$ that proves the model is fitted quite well. The results show that only CF is not significant with $p<0.001$; however, it is significant with $p<0.1$. Considering the quadratic term, only MNIL is significant. At the confidence level of 99.9%, the interaction between MNIL and FS is statistically meaningful. Again it can be claimed that the hyper-parameter cannot be optimized independently from the feature selection strategy, as there is considerable interaction, which is a contribution of this study. Considering the maximization of AUC and the minimization of SoT, the optimum values of the parameters of C4.5, differ from their default values. The optimum values of MNIL and CF are 42 and 0.31, respectively. Also, the feature selection is not suggested, and the binary split did not affect the performance of the C4.5.
The decision tree created by the tuned CART is shown in Fig. 4. The size of tree is 13, which consisted of 5 features and 7 leaves. Each leaf provides a rule for profiling GPs’ prescribing patterns. For each rule, the first number in parenthesis indicates the total number of instances (GPs) identified by the rule, while the second one is the number of instances by which the rule is misclassified (number of instances/number of misclassifications). For example, it can be seen that rule No. 5 (R5) distinguished 1089 GPs as who has prescribed more than 3 drugs per encounter averagely. However, 293 GPs, who prescribed normally, were misclassified by the rule. More information on the 4 rules that identified polypharmacy is given in Table 3. It can be seen that only R5, which consists of only two features, has been able to detect more than 71% of polypharmacy cases with a confidence of 73%.

Similarly, the decision tree generated by the tuned C4.5 is depicted in Fig. 5. The size of tree is 23, including 7 leaves and 9 features. The decision tree is relatively more complex than the one created by the tuned CART. However, there are only 4 rules for identifying polypharmacy that is similar to CART. Table 4 gives more information on the interestingness of these rules. Just R11, which is composed of only two features, has identified about 71% of cases of polypharmacy. It has more than 78% confidence.

Furthermore, the rules generated by CART and C4.5 and recognized polypharmacy are expressed in a verbal form in order of interestingness measures as follows to make them more transparent for healthcare experts and policy-makers.

- **CART**

  R5: If the average number of dispensed prescriptions per pharmacy of a GP is greater than or equal to 5.135 and the percentage of female patients is not too much (approximately less than 70%) then polypharmacy has occurred.

  R1: If the average number of dispensed prescriptions per pharmacy of a GP is less than 5.135 and the percentage of his young adult patients aged between 15 and 29 years old is small (approximately less than 6%), then he prescribes excessively (more than 3 drugs per encounter).

  R4: If the average number of dispensed prescriptions per pharmacy for a GP is between 2.075 and 5.135 and both the percentage of his patients aged between 5 and 14 years old and the percentage of his patients aged between 15 and 29 years old are not small (approximately more than 6.7% and 5.8% respectively) then polypharmacy has occurred.

  R7: If for a GP, the average number of dispensed prescriptions per pharmacy is greater than or equal to 5.135 and the percentage of his patients aged less than 5 years old is not very small (approximately more than 2.2%), and percentage of female patients is not too much (approximately less than 70%) then he prescribed abnormally.

- **C4.5**

  R11: If the average number of dispensed prescriptions per pharmacy of a GP is greater than 5.13 and the percentage of his patients aged less than 5 years old is approximately less than one quarter (≤26.17%), and the percentage of male patients is not too insignificant (approximately more than 4.1%) then polypharmacy has occurred.

  R7: If the average number of dispensed prescriptions per pharmacy of a GP is less than or equal to 5.13 and the percentage of his patients aged less than 5 years old is less than or equal to
30% and the percentage of his elder patients aged between 70 and 94 years old is roughly more than 24.3%, and the percentage of patients in the rural insurance fund is insignificant (approximately less than 4.7%) then he prescribes excessively.

R4: If the average number of dispensed prescriptions per pharmacy of a GP is less than or equal to 5.13 and the percentage of his child patients (less than 5 years old) and elderly patients (between 70 and 94) is roughly less than or equal to 30% and 24.3%, respectively while the percentage of his young adult patients (between 15 and 29 years old) is not insignificant (is more than 6%), and the percentage of male patients is approximately more than or equal to 23.5% and the total number of pharmacies that dispensed his prescriptions is less than 24, and the total number of prescriptions is more than 32 then the GP prescribed abnormally.

R5: If the average number of dispensed prescriptions per pharmacy of a GP is less than or equal to 5.13 and the percentage of his child patients (less than 5 years old), middle-aged patients (between 30 and 49), and elderly patients (between 70 and 94 years old) is roughly less than or equal to 30%, 18%, and 24.3%, respectively and the percentage of male patients is approximately more than or equal to 23.5%, and the total number of pharmacies that dispensed his prescriptions is bigger than 23 then polypharmacy has occurred.

On the other hand, various performance measures have been calculated for the applied algorithms with the tuned configuration as well as default ones, the summary of which is presented in Fig. 6. It can be seen that the parameter tuning had a significant improvement in the AUC and the accuracy of the C4.5 and result in smaller tree. The default setting of C4.5 generated a huge tree with 443 nodes and 233 leaves. In other words, by adjusting the parameters, not only the performance indicators of the C4.5 have been improved but also a smaller and more understandable tree has been created. The CART parameters setting resulted in a smaller tree, whereas the untuned CART generated a tree with 21 nodes and 11 leaves. However, it caused a decline in AUC and TNR (specificity), while it increases TPR (recall). It is important to note that in this case, bigger TPR is preferable to bigger TNR. Because the costs of misclassification are not the same in the two classes, in other words, if a GP, who prescribes normally, be misclassified as a physician who prescribes excessively, then it will eventually lead to more training or some strict policies, which can lead to more rationalization use of drugs. Conversely, if a GP with an anomalous prescribing pattern is not correctly distinguished, he may continue his abnormal behavior.

Since the end-users should evaluate whether the extracted rules are interesting and useful, they were subject to judgment by experts from the Iran Healthcare Insurance Organization. Given that they have not experienced such a data mining approach to examine the rational use of drugs, the results were generally welcomed by them. Also, many extraction rules were considered useful. For example, they confirmed that the presence of a strong relationship between a physician and some pharmacies could lead to excessive drug prescription and abnormal behavior. Although some rules, such as R5 of C4.5, which stated the association with more pharmacies (more than 23) might cause polypharmacy, is not tangible. In other words, it was expected that a partnership with fewer pharmacies would cause polypharmacy. In general, the experts preferred the more easy-to-follow CART rules that made it more perceptible.

5. Conclusions

WHO and INRUD suggest that the ‘average number of drugs prescribed per encounter’ could
be used to appraise the extent of polypharmacy. Decreasing polypharmacy exposure can decline risks of adverse drug reactions (ADRs), adverse drug events (ADEs), prescribing potentially inappropriate medications (PIM), mortality, and other dangerous consequences. In this paper, to the best of authors’ knowledge, the first data mining framework was developed to study polypharmacy. The approach contains three steps: pre-modeling, modeling, and post-modeling. Pre-modeling includes collecting data, handing inconsistent data, integrating of different data sources, and extracting several features. In the modeling step, C4.5 and CART were applied to build models to elicit a set of rules for polypharmacy detection and explanation. To improve the performance of utilized decision trees, their parameters were tuned by RSM to maximize AUC and minimize SoT using the desirability function approach along with the CFS method of feature selection simultaneously. The results demonstrated that the hyper-parameter cannot be independently optimized from the feature selection strategy, as there is considerable interaction between them. Also, the tuned C4.5 created a smaller tree and improved the accuracy and AUC compared to the untuned one. Furthermore, tuned CART, generated a smaller tree; however, its TNR (specificity), accuracy, and AUC declined. On the other hand, its TPR (sensitivity) increased to 84.5%. TPR measures the algorithm’s capability in detecting polypharmacy. According to both C4.5 and CART, ‘the average number of dispensed prescriptions per pharmacy’ is the key feature for identifying polypharmacy. It shows the extent of the relationship between physicians and pharmacies. Also, patient age groups and patient gender are effective features. However, physician gender and experience have not noticeable effect on prescribing patterns. In the final step, the extracted rules for polypharmacy detection were visualized and simplified and then were presented to domain experts to evaluate them. In general, they preferred the rules created by CART because of its transparency and simplicity.

This study demonstrates the data mining approach’s capabilities to analyze and describe the GPs’ prescribing pattern in association with polypharmacy. The approach can determine GPs’ profile as a set of If-Then rules; therefore, it can be used as a part of an automatic drug prescription monitoring system. It could also be helpful for healthcare managers and policy-makers to understand the factors associated with physicians’ prescribing pattern to take suitable action and improve appropriate prescribing affairs to decline the average number of drugs prescribed per encounter, optimize drug regimens for patients, support high quality prescribing, and develop or revise prescribing guidelines.

In the future studies, in the case of access to physicians' supplementary data, such as age, academic records, work history, place of prescription, they can be included in the data mining procedure. Also, over the counter (TOC) drugs, dietary supplements, and complementary and alternative medicine (CAM) can be considered in the analysis; however, gathering this kind of data is very difficult and time-consuming. Furthermore, medical diagnosis and inpatients’ prescriptions data can be involved to enrich the results. Since in the literature, different cutoff numbers are used for defining polypharmacy; they can be applied for sensitivity analysis. In this research, the threshold of three drugs is used in the definition of polypharmacy. The consideration of five or more drugs as definition threshold results in facing to an imbalanced dataset, which make the analysis more technically appealing. Besides, the proposed method can be generalized to analyze other WHO’s measures of rational use of drugs such as the percentage of prescriptions containing antibiotics, the percentage of encounters prescribed Injection, and the percentage of drugs prescribed from PHC formulary. The values of some features can be fuzzified to make the results more understandable for the healthcare managers and policy-makers.
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Fig. 1. Proposed data mining procedures

Fig. 2. Central composite designs for $k = 2$

| Actual Class | Predicted class |
|--------------|----------------|
| Positive     | Positive       | Negative       |
| Positive     | True positive (TP) | False negative (FN) |
| Negative     | False positive (FP) | True negative (TN) |

Fig. 3. Confusion matrix
\( \text{APpPn} < 5.135 \)
\[
\begin{align*}
& \mid \text{PpAG1} \leq 0.300884 \\
& \mid \text{PpAG6} \leq 0.243055 \\
& \mid \text{PMPa} \leq 0.2353294: 0 \ (143.0 / 22.0); \text{R1} \\
& \mid \text{PMPa} > 0.2353294 \\
& \mid \text{TPPa} \leq 23 \\
& \mid \mid \mid \text{PpAG2} \leq 0.066815: 0 \ (224.0 / 95.0); \text{R2} \\
& \mid \mid \mid \text{PpAG2} > 0.066815 \\
& \mid \mid \mid \text{TPPa} \leq 32: 0 \ (47.0 / 21.0); \text{R3} \\
& \mid \mid \mid \mid \text{TPPa} > 32: 1 \ (100.0 / 21.0); \text{R4} \\
& \mid \mid \mid \text{TPPa} > 32 \leq 23 \\
& \mid \mid \mid \mid \text{PpAG4} \leq 0.179487: 1 \ (59.0 / 26.0); \text{R5} \\
& \mid \mid \mid \mid \text{PpAG4} > 0.179487: 0 \ (507.0 / 147.0); \text{R6} \\
& \mid \mid \mid \mid \text{PpAG6} \leq 0.243055 \\
& \mid \mid \mid \mid \text{PpAF3} \leq 0.046875: 1 \ (140.0 / 30.0); \text{R7} \\
& \mid \mid \mid \mid \text{PpAF3} > 0.046875: 0 \ (47.0 / 20.0); \text{R8} \\
& \mid \mid \mid \mid \text{PpAG1} > 0.300884: 0 \ (37.0); \text{R9} \\
& \mid \mid \mid \text{TPPa} > 0.040816: 0 \ (46.0 / 1.0); \text{R10} \\
& \mid \mid \mid \text{TPPa} > 0.040816 \\
& \mid \mid \mid \mid \text{PpAG1} \leq 0.261718: 1 \ (1422.0 / 308.0); \text{R11} \\
& \mid \mid \mid \mid \mid \text{PpAG1} > 0.261718: 0 \ (25.0 / 6.0); \text{R12} \\
\end{align*}
\]

**Fig. 4.** The decision tree generated by tuned CART

**Fig. 5.** The decision tree generated by tuned C4.5

**Fig. 6.** Performance measures of applied decision trees
### Table 1: Dataset attributes

| Attribute                        | Symbol | Data type | Value       | Role       |
|----------------------------------|--------|-----------|-------------|------------|
| Gender                           | Gender | Binary    | 0, 1        | Input      |
| Experience                       | Experience | Nominal | 1, 2, 3, 4 | Input      |
| Total number of patients         | TNPa   | Numeric   | ≥ 1         | Input      |
| Percentage of female patients    | PFPa   | Numeric   | [0,100]     | Input      |
| Percentage of male patients      | PMPa   | Numeric   | [0,100]     | Input      |
| Percentage of patients in age group $i$ | PPaAG$_i$ | Numeric | [0,100]     | Input      |
| Percentage of patients in the $i$-th insurance fund | PPaF$_i$ | Numeric | ≥ 24        | Input      |
| Average number of prescriptions per patient | ANPP | Numeric   | ≥ 1         | Input      |
| Total number of pharmacies       | TNPh   | Numeric   | ≤ 1         | Input      |
| Average number of prescriptions per pharmacy | APrPh | Numeric   | ≥ 1         | Input      |
| Polypharmacy                     | PP     | Binary    | 0, 1        | Class      |

### Table 2: Primary hyper-parameters of C4.5 and CART

| Algorithm | Hyper-parameter | Symbol | Possible Value | Type | Default |
|-----------|----------------|--------|----------------|------|---------|
| CART      | minimum number of instances per leaf | MNIL   | ≥ 1            | integer | 2       |
| CART      | percentage of training data used to construct the tree | PTD    | (0, 1]         | real  | 1       |
| CART      | using 1 SE rule to make pruning decision | 1SEr   | {False, True}  | logical  | False   |
| C4.5      | confidence factor | CF     | [0.001, 0.5]   | real  | 0.25    |
| C4.5      | minimum number of instances per leaf | MNIL   | ≥ 1            | integer | 2       |
| C4.5      | binary splits | BS     | {False, True}  | logical  | False   |

### Table 3: Rules generated by CART for identifying polypharmacy

| Rule No. | Rule | No. of Features | Support (%) | Coverage (%) | Confidence (%) |
|----------|------|----------------|-------------|--------------|----------------|
| R1       | APrPh < 5.135 and PPaAG1 < 0.058055 and PPaAG2 > 0.066815 and PPaAG6 ≥ 0.243055 and PMPa ≥ 0.235294 and TNPh ≤ 23 and TNPv > 32 | 2       | 2.1           | 3.8            | 27.6           |
| R4       | 2.075 ≤ APrPh < 5.135 and PPaAG2 < 0.0670405 and PPaAG3 > 0.058055 | 3       | 1.8           | 3.3            | 24.3           |
| R5       | APrPh ≥ 5.135 and PPaAG1 ≤ 0.0226805 and PMPa ≥ 0.235294 and TNPh ≤ 23 and TNPv > 32 | 2       | 39.2          | 71.3           | 73.1           |
| R7       | APrPh ≤ 5.135 and PPaAG1 ≥ 0.0226805 and PMPa ≥ 0.7051145 | 3       | 0.4           | 0.8            | 40.9           |

### Table 4: Rules generated by C4.5 for identifying polypharmacy

| Rule No. | Rule | No. of Features | Support (%) | Coverage (%) | Confidence (%) |
|----------|------|----------------|-------------|--------------|----------------|
| R4       | APrPh ≤ 5.135 and PPaAG1 ≤ 0.300884 and PPaAG2 > 0.066815 and PPaAG6 < 0.243055 and PMPa > 0.235294 and TNPh ≤ 23 and TNPv > 32 | 7       | 2.82          | 4.8            | 79.0           |
| R5       | APrPh ≤ 5.135 and PPaAG1 ≤ 0.300884 and PPaAG4 ≤ 0.179487 and PPaAG6 ≤ 0.243055 and PMPa > 0.235294 and TNPh > 23 | 6       | 1.18          | 2.0            | 55.9           |
| R7       | APrPh ≤ 5.135 and PPaAG1 ≤ 0.300884 and PPaAG6 > 0.243055 and PMPa ≥ 0.046875 and PMPa < 0.046875 | 4       | 3.93          | 6.7            | 78.6           |
| R11      | APrPh > 5.135 and PPaAG1 ≤ 0.261718 and PMPa > 0.040816 | 3       | 39.83         | 67.8           | 78.3           |