UNDER PEER REVIEW

Short Research Article

Effect of Drug-Drug Interactions by Association Rule Discovery among the Elderly

ABSTRACT

Objective: With the decline of the bodily function, the elderly increased polypharmacy frequency. The results lead to the danger of duplicate drug and the risk of drug interactions. In this paper, the effect of drug-drug interactions studied for the elderly living in Taiwan.
Methods: The association rules and hypothesis testing technology were proposed to analyze the impact of drug-drug interactions. The real case for a teaching hospital in Taiwan as a case study.
Results: From the analysis, shown three results. (1) Four out of 100 patients have the threat of drug interactions. (2) The proportion of drug-drug interactions is highest in the cardiovascular medicine, and (3) the number of drug-drug interaction for elderly is 2.01 times of the other people.
Conclusion: The study suggests that the public should describe their medications to medical staffs spontaneously to help doctors to reduce the incidence of drug interactions and drug wastage.

Keywords: Data Mining; Risk of Medication; Decision Rule

1. INTRODUCTION

Definition of drug interactions is a kind of adverse drug reaction. When the patient takes two or more kinds of medicine at the same time, the pharmacological or clinical results are different from the expected ones [1]. The medicine would not perform the expected cure and could worsen the patient's condition or lead to his death. There are three types of drug interactions: drug-drug interactions, drug-food interactions, and Drug-condition interactions [2]. Drug-drug interactions refer to two or more kinds of medicine taken by the patient at the same time and the medicine he takes to produce interference that causes unexpected effects and then influences the medicine taker's condition. Drug-drug interactions can further categorize into antagonism. The drug items reduce or increase the impact of another one. Drug-food interactions are the interactions between medicine and food (or beverage) that could change the effects of the drug when Drug-condition interactions refer to the interactions between conditions and some medications.

Taiwan has become the other rapidly aging society in the world only to Japan. People aged over 65 years old for 14% of our population, and the percentage is expected to increase rapidly in 2020. The percentage of medical care of elders is expected to rise rapidly in the future to come. With the growth of age, the deteriorating physical functions, biological aging, pharmacokinetics or pharmacodynamics in nature, and multi-organ degeneration are increasing the chances of suffering multiple chronic diseases for the elder. Besides, the private patients used to receive treatments and medicines across hospitals enhance the risk of polypharmacy, resulting the elder is a high-risk population of patients with drug interactions.

A study conducted on 1,601 people in Europe pointed out that 46% of patients have at least one potential significant interaction, and 10% of them are of high severity [3]. According to the reported by Taiwan Shin Sheng Daily News on October 7th, 2009. The possibility of drug interactions with the elders is 2.5 times as much as average men, and the repeated prescription wasted 2.7 billion NT dollars of National Health Insurance in Taiwan. Therefore, it is important to discuss drug integrations issues among older adults in Taiwan. The quality of medical care will be enhanced effectively if data analysis can provide the severity and proportion of drug interactions. The analysis results can serve as useful references for medical units.

UNDER PEER REVIEW

Figure 1 show the summary of previous studies on drug interactions. Most of the researchers still aim at the incidence, severity, and modification rate of physician and interactions of drugs as exploring direction. However, previous studies often failed to make a complete investigation of different divisions and characteristics. Therefore, this study analyzes the database data from the teaching hospital in Taiwan and used associated rules and statistical analysis to provide useful references for medical units.

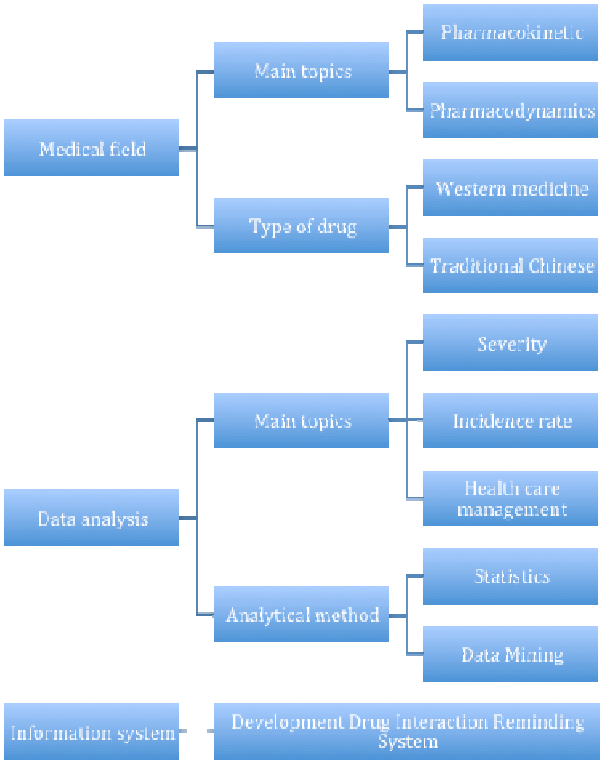

Fig. 1. A summary of previous studies on drug interactions

2. METHODS

The analytical procedures in this study contained three major parts. In the first part, Microsoft Access was used for data preprocessing. Moreover, the second part included analyzes of the incidence and severity of drug interactions and drug interaction differences between various medical specialties. Finally, SQL Server 2008 R2 was used to generate association rules for gender, age, medical specialty, diagnosis codes, and drug interactions. Such rules can use as a future reference for medical institution management.

First of all, the medical records of the patients and drug interaction files were joined to obtain the data for analysis. The data of patient medical history not directly exported from the database in the teaching hospital. Thus, a database analysis was not able to proceed in the prescription. For this reason, the Microsoft Access has performed the data format conversion. The steps were as follows:

- **Step 1: Matrix Transformation**

As shown in figure 2, Matrix multiplication obtained 2, one-to-one correspondences between medical record files of the patients and prescription drugs. The oblique, bold text represented the right drug combinations for drug interaction.

- **Step 2: Data Matching**

UNDER PEER REVIEW

After the matrix conversion had completed, the tables of drug matchings' and drug interactions were compared in figure 3 and the matching result shown in drug interactions. The oblique, bold text in figure 4 described level 2 drug interactions. The matching results were analyzed and provided the empirical results.

ID	Drug
1	A
1	B
1	C
2	A1
2	B1
2	C1

×

ID	Drug
1	A
1	B
1	C
2	A1
2	B1
2	C1

=

ID	Drug	ID	Drug
1	***A***	***1***	***A***
1	***A***	***1***	***B***
1	***A***	***1***	***C***
1	A	2	A1
1	A	2	B1
1	A	2	C1
1	***B***	***1***	***A***
1	***B***	***1***	***B***
1	***B***	***1***	***C***
1	B	2	A1
1	B	2	B1
1	B	2	C1
…	…	…	…

Fig. 2. The Example of Matrix Transformation

ID	Drug	ID	Drug
1	A	1	A
1	A	1	B
1	A	1	C
1	B	1	A
1	B	1	B
1	B	1	C
…	…	…	…

↔

Drug	Drug2	Interaction
B	C	2

Fig. 3. The Example of Data Matching

ID	Drug	Drug2
1	A	B
1	A	C
1	***B***	***C***
2	A1	B1
2	A1	C1
2	B1	C1

Drug	Drug2	Interaction
B	***C***	***2***

UNDER PEER REVIEW

Fig. 4. The Example of Matching results

The analysis methods adopted in the second part included a Pareto analysis and a chi-square test for independence to examine the drug interaction differences between various medical specialties.

In the third part, association rule mining was used to explore the relationships between different variables or entities in the database by a probability calculation. Association rules were defined as follows [4].

Let $I=\{I_1,I_2,\ldots I_m\}$ be a set of m commodity items.

Let $D=\{t_1,t_2\ldots t_n\}$ be a set of transactions of n clients, where $t_i=\{I_{i1},I_{i2},\ldots I_{ik}\}$ stands for the transaction data of the ith client.

During the process of association rules mining, the rules generated may significantly increase due to the excessive number of item combinations. Agrawal and Srikant's proposed Apriori algorithm to allow the users to gain valid rules efficiently [5]. The followings described the calculation steps of patients' prescriptions in this study. The concept map presented in Fig. 5.

- Step 1: Calculate the support of drug items according to each patient's prescription. Drug itemset 1 was obtained.
- Step 2: Screen out the items in Drug itemset one that failed to satisfy the minimum support (set at 1). Drug itemset 2 was obtained.
- Step 3: List all the possible 2-item combinations using the items in Drug itemset 2 to form Drug itemset 3. Calculate the support of each combination.
- Step 4: Repeat Step 2 to dispose of the items in Drug itemset three that failed to meet the minimum support.
- Step 5: Repeat the steps above to generate the "maximal frequent itemset."

UNDER PEER REVIEW

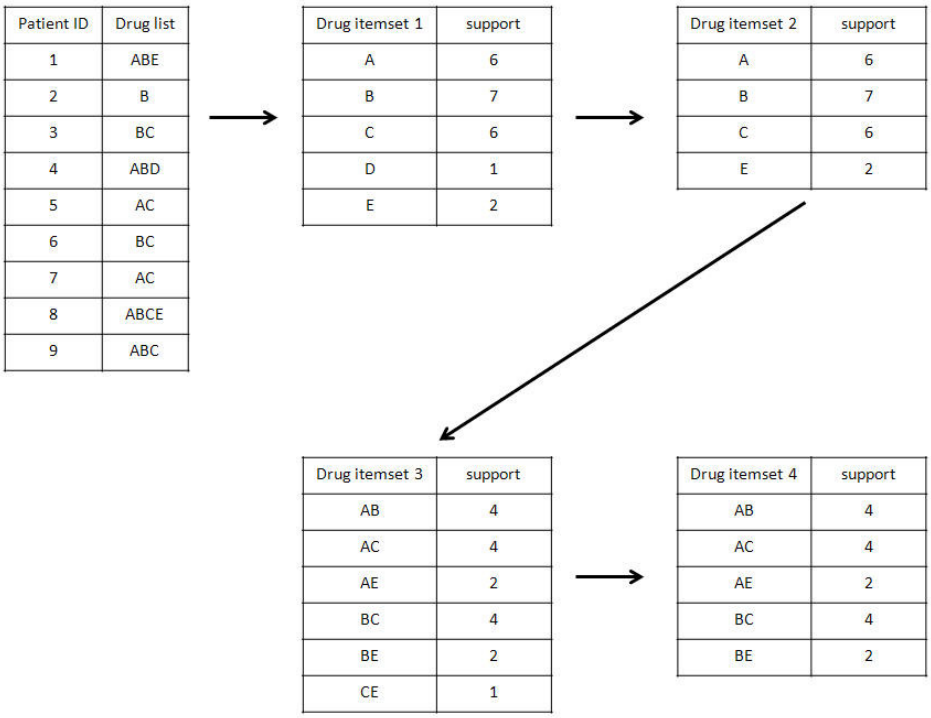

Fig. 5. The Example of Process of Apriori algorithm

Support, confidence, and importance were served as significant indicators in this study to identify association rules. Support denoted the probability of purchasing X and Y simultaneously; confidence the probability of obtaining Y when X is obtained. Suppose the support of "Drug A→Drug B" was 0.25 and the confidence was 0.714. In this case the probability of Drug A and Drug B occurring jointly in a prescription was 25%; the probability of Drug B being prescribed when Drug A was prescribed was 71.4%. The importance index was generated by calculating the logarithmic value of the number obtained by dividing "the rate of Y with the presence of X" by "the incidence of Y with the absence of X" [6].

3. ANALYSIS RESULTS

Regarding the characteristics of the original data, there are totally 59 treatment divisions, including the division of general medicine and general medicine, the division of pediatrics, and the distribution of cardiology and cardiovascular surgery. The total number of consultation records is 588,316. The youngest age of patients is 2, and older age is 108. Among 588,316 consultation records, there are more women than men with a 51.26% percentage of females. Elderly people account for 30% of people of all ages. On the other hand, the general outpatient clinic consultations account for 90.85% of all types of clinical consultations.

First, an investigation of the severity and incidence rate of drug interactions in all patient consultation records is made. Regarding the incidence rate, among all patients, 21,721 patients have drug interactions; which generates an incidence rate of approximately 4%. There are 51.31% of these patients are men, which is slightly higher than women proportionally. A confidence interval test is further conducted. Given a 95% confidence level, the incidence rate of drug interactions makes that four out of one hounded patient are under the risks of drug interactions. Among 21,721 patients, there are 11,753 elderly patients aged 65 and above who have drug interactions. The percentage is 54.1%, which shows significant differences. Regarding severity, after matching with the database of drug interactions, 25,151 drug combinations entail risks of creating drug interactions. There are evidently more outpatient clinic cases (96%) than emergency ones (4%). Concerning the emergency treatment alone, the division of general medicine shows the highest percentage of 96.62% whereas gynecology shows the lowest with

UNDER PEER REVIEW

0.3%. Among 25,151 combinations, the proportions of significance grade 1 and two drug interactions are 28.82% and 71.18% respectively. There is no significant difference found between genders.

Concerning drug interactions in different divisions, of all patients' consultation records, the proportion of patients in the department of cardiovascular surgery is the highest (15.96%) while the percentage of patients in the family medicine clinic is the second highest (13.54%). The percentage of cardiology patients, immunology and rheumatology patients, and the patients in the division of infectious diseases are 11.63%, 10.33% and 8.06%, respectively. Among elderly patients aged 65 and above, cardiology patients accounts for the highest proportion of all (43.9%). Next to the highest are the percentages of neurology patients (14.3%) and cardiovascular surgery patients (12.7%). A chi-square test of independence is further conducted to analyze the differences in drug interactions among different divisions of medicine. The result shows that p-value=0. 000, which implies that regarding all patient consultation records of patients aged 65 and above, there are significant differences in drug interactions among different divisions of medicine.

Regarding the severity of drug interactions among elderly patients (aged 65 and above) in various departments of medicine. The divisions with higher incidence rates of grade 1drug interactions are the division of cardiology (49.4%) and the department of cardiovascular surgery (28.6%), which account for nearly 80% of elderly patients. The three divisions with higher incidence rates of grade 2 drug interactions are cardiology (41.4%), neurology (19.4%), and metabolism (17.1%).

About the gender differences in elderly patients' drug interactions in different divisions. For male patients, the divisions with higher incidence rates of grade 1 drug interactions are cardiovascular surgery (26.5%) and cardiology (51.6%); whereas for female patients, the divisions are cardiovascular surgery (47.3%) and cardiology (30.6%). For both male and female patients, these two divisions account for 80% of all cases. Regarding grade 2 drug interactions. For male patients, the three divisions with higher incidence rates are cardiology (42.1%), neurology (22.8%), and metabolism (12.7%); whereas for female patients, the top three divisions are cardiology (40.8%), metabolism (21.1%), and neurology (16.4%).

As for the age trend of drug interactions, results of grade 1 drug interactions are illustrated in Figure 6. As age grows, drug interactions increase quickly. From the ages of 31-40 to the ages of 61-70, there is a higher proportion of male patients than the percentage of female patients. From the ages of 71-80, this situation declines as the number of elderly patients varies. Results of grade 2 drug interactions show in Figure 7. Similar to grade 1 drug interactions, as age grows, patients increasingly suffer from grade 2 drug interactions at age 50. The increasing rate for male patients is far faster than it is for female patients. A chi-square test of independence is conducted to analyze the correlations between age and the incidence rate of drug interactions. The result shows that p-value=0.000, which implies that age correlates with the incidence rate of drug interactions.

UNDER PEER REVIEW

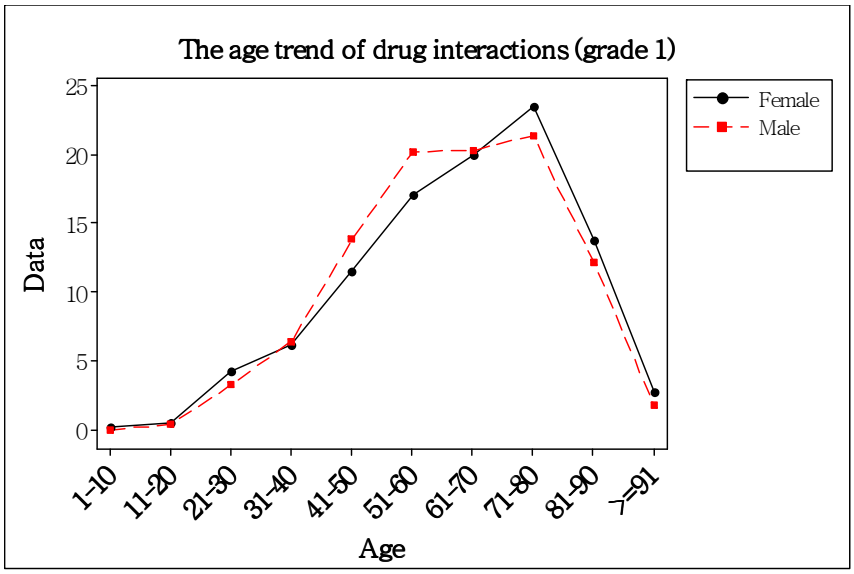

Fig. 6. The age trend of drug interaction (grade 1)

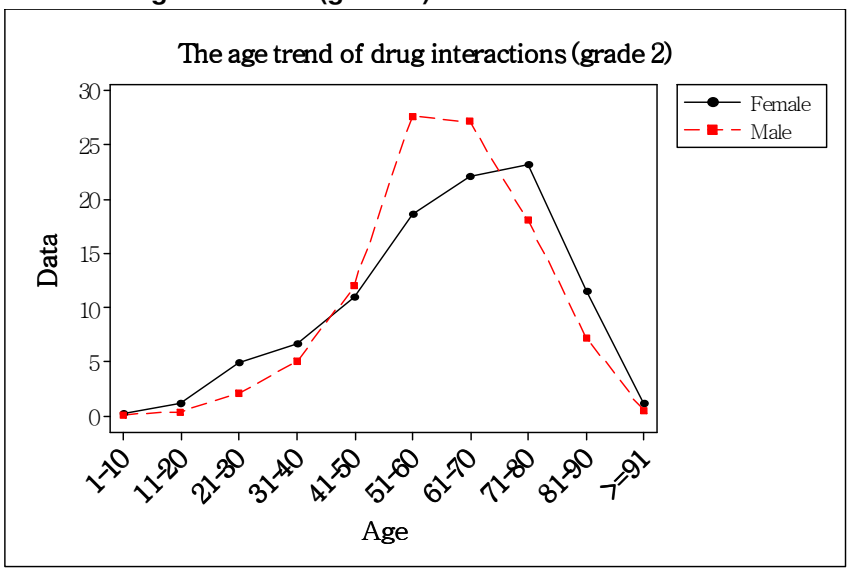

Fig. 7. The age trend of drug interaction (grade 2)

A chi-square test of independence alone cannot indicate the strength of correlations between patients' age and drug interactions. Therefore, the present study uses odds ratios to conduct a test. The results show: patients aged 65 and above are twice more likely than their counterparts under 65 years old to suffer from drug interactions (95%CI, 1.9593-2.0691).

Following this, association rule mining is conducted on patient's aged 65 and above. The minimum support set to 10. The confidence level is 80 to eliminate other rules. The analysis finds two rules that are as follows.

- Result 1: the association rules of Cardiology

  Furosemide and Digoxin often prescribed for patients in cardiology at the same time. Regardless of gender differences, both male and female patients would suffer from grade 1-drug interactions due to the combination of these two drugs.

- Result 2: the association rules of Cardiology

UNDER PEER REVIEW

Aspirin and Digoxin often prescribed for patients in cardiology at the same time. Regardless of gender differences, both male and female patients would suffer from grade 2 drug interactions due to the combination of these two drugs.

4. CONCLUSION

Previous studies often failed to make a complete investigation of the differences in drug interactions among older people of different divisions and characteristics. Therefore, this study explores the association between drug interactions in various departments and prescriptions for patient's aged 65 and above. The database of a teaching hospital in north Taiwan is used. After analysis, five conclusions are derived. (1) The incidence rate of drug interactions in all patients' consultations records is approximately 4% given a 95% confidence level, which implies that four out of one hundred patients are under the risks of drug interactions. (2) Regarding the incidence rates of drug interactions for patients aged 65 and above in different divisions, cardiology patients are most likely to suffer from drug interactions. (3) As for the incidence rates of grade 1 drug interactions of elderly patients in different divisions and of different genders. The highest rates for both male and female patients found in departments of cardiology and cardiovascular surgery, which account for nearly 80% of all cases. (4) Regarding the trends of age and drug interactions, patients of both genders share an increasing trend in grade 1 and two drug interactions from the ages 41-50. An odds ratios analysis examines the incidence rates of drug interactions for patients of different ages. The results show that the incidence rate of drug interactions for patients aged above 65 is 2.01 times higher than the rate for patients under 65 years old. (5) Regarding the association rules of the consultation database for patients aged 65 and above, the analysis generates two crucial roles regarding drug items and treatment divisions. Results find that some drug items strongly associated with individual departments. In other words, when patients receive treatments in different departments, doctors usually prescribe some medications that may easily induce drug interactions. This situation requires attention.

This study aims to reveal the severity and the incidence rate of drug interactions in Taiwan through database analysis. Research findings show that if data aggregation pretreated through association rules, medical institutions could be informed with useful information in establishing drug interaction warning systems. Besides, the incidence rate of drug interactions for patients aged 65 and above is 2.01 times higher than it is in patients under 65 years old, which indicates that medical institutions should pay attention to the problem of drug interactions among elderly patients.

Finally, this study suggests that the public should describe their medications to medical staffs spontaneously to help doctors to reduce the incidence of drug interactions and drug wastage.

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