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

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Authors' contributions

This work was carried out in collaboration between both authors. Authors CCW and JCC designed the study, wrote the protocol and wrote the first draft of the manuscript. Author JCC collected the data and searched for the literatures. Authors CCW and JCC analyzed the results. Both authors approved the final manuscript.

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Short Research Article

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ABSTRACT

Objective: With the decline of the bodily function, the elderly increased polypharmacy frequency. The results lead to the danger for duplicate drug and drug interactions (DDIs). This study aims to analyze the effect of DDIs of the elderly in Taiwan.
Methods: The association rules and hypothesis testing technology were proposed to analyze the impact of drug-drug interactions, using the real cases in Taiwan Teaching Hospital.
Results: From the analysis, shown three results. Firstly, four out of 100 patients have the threat of drug interactions. Secondly, the proportion of drug-drug interactions is highest in the cardiovascular medicine. Thirdly, the number of drug-drug interaction for elderly is 2.01 times of the other people.
Conclusion: I suggested that the patient should be reminded to describe their medications for medical staffs spontaneously to help doctors for reducing the risk of drug interactions and drug wastage.

Keywords: Data mining; risk of medication; decision rule.

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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 [1-2]. The medicine would not perform the expected cure and could worsen the patient's condition or lead to his death. The drug-drug interactions, drug-food interactions, and Drug-condition interactions are the three most common types of interaction [3]. The drug and drug interactions refer to events in which the unexpected effects of pharmacological when two drugs are administered simultaneously or within a short time of each other. The drug and drug interactions may decrease or increase the effect of another one or both drugs. Drug-food interactions refer to the between medicine and food (or beverage) that could change the effects of the drug. Drug-condition interactions relate to the interactions between conditions and some, may occur when an existing medical condition makes certain drugs potentially harmful [4]. 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, 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 [5-8]. About the analyze drug-drug interactions, Lu et al. proposed a random-sampling-based statistical algorithm to identify possible drug-drug interactions, using the MEDLINE literature for underlying mechanism [9]. Toivo et al. used online drug-drug interactions surveillance system to identifying high-risk medications causing potential drug-drug interactions in Finnish community pharmacies [10].

In a European study of 1,601 medical outpatients analyze finding that 46% have at least one potential significant interaction, with 10% of these interactions regarded as of high severity [11]. According to the report 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 NT $2.7 billion 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 information for improving prescription quality by the doctor.

Fig. 1 shows the summary of previous studies on drug interactions. Most of the researchers focused on the incidence, severity, and modification rate of the physician as the exploring direction for drug and drug interactions. Nevertheless, previous research often failed to make a complete investigation of different department and characteristics. In this paper, proposed the associated rules and statistical analysis to analyze the data obtained from the teaching hospital in Taiwan, the result can provide useful references for medical units.

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, the Microsoft SQL Server 2008® 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.

In this paper, using the real data in Taiwan Teaching Hospital to analyze the effect of DDIs among the elderly. Table 1 represents the relationship between the level of DDIs. 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. Therefore, an original database was not able to proceed in the prescription. For this reason, the Microsoft Access® has performed the data format conversion.

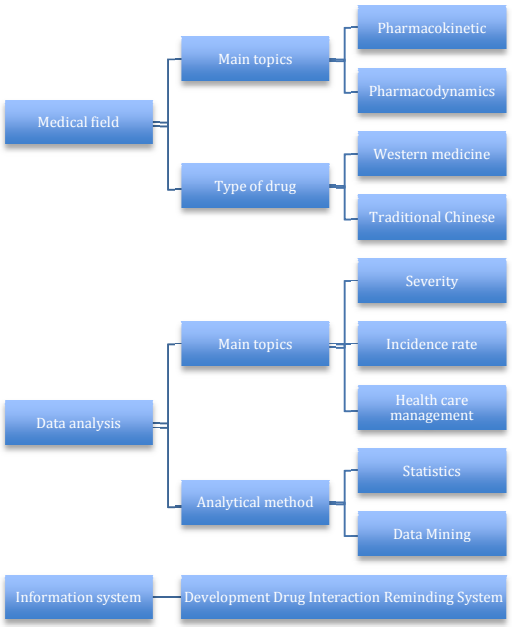


Fig. 1. A summary of previous studies on drug interactions [12]

Table 1. The relationship between the level of drug and drug interactions

Drug code 1	Drug interaction name 1	Drug code 2	Drug interaction name 2	Level
IAMIK5	Amikacin sulfate	IAMPI5	Ampicillin	2
IAMIK5	Amikacin sulfate	IATRI2	Atracurium Besylate	1
.	.	.	.	.
.	.	.	.	.
OWARF5	Warfarin sodium	OVITE4	Vitamin E	1

The data pre-process steps were as follows:

Step 1: Matrix Transformation

Fig. 2 shown the Matrix multiplication obtained 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.

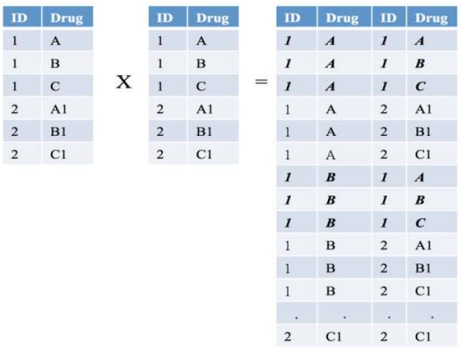


Fig. 2. The example of matrix transformation

Step 2: Data Matching

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

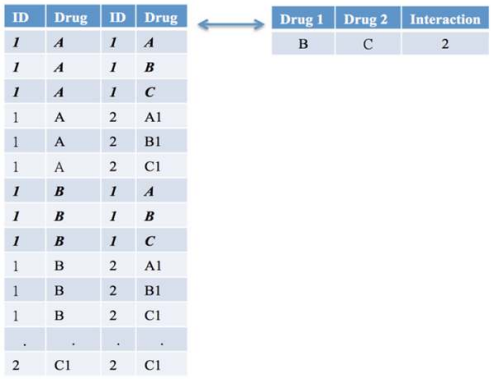
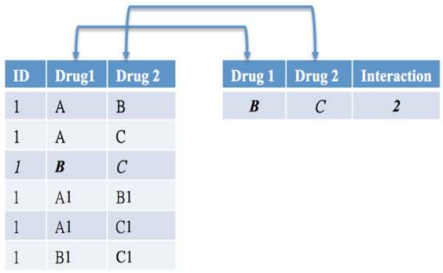


Fig. 3. The example of data matching



ID	Drug1	Drug 2
1	A	B
1	A	C
1	***B***	*C*
1	A1	B1
1	A1	C1
1	B1	C1

Drug 1	Drug 2	Interaction
B	*C*	*2*

Fig. 4. The example of matching results

The analysis methods adopted the Pareto analysis and a chi-square test in the second part. Pareto analysis was used to sort the effect of DDIs in the different medical divisions. A chi-square test for independence was adopted 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 entities in the database by a probability calculation. Association rules were defined as follows [13].

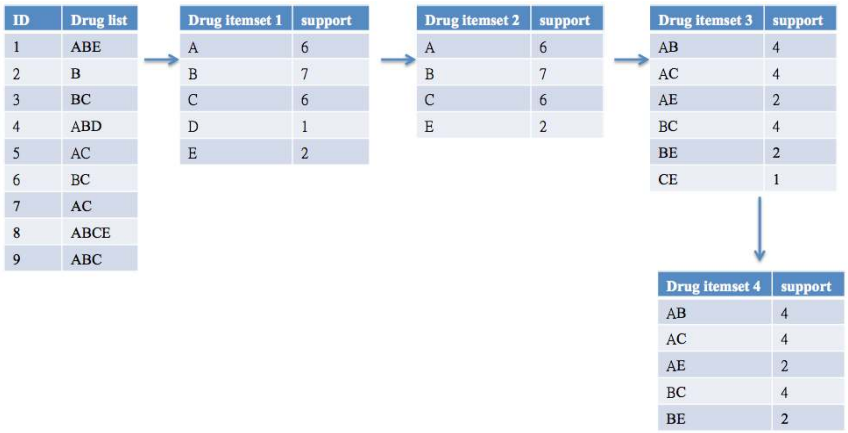
Let $I=\{I_1,I_2,\ldots I_m\}$ be a set of m commodity items.

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 i^{th} client.

The rules generated will significantly increase due to the excessive number of item combinations in the data mining process of the association rule. Agrawal and Srikant's proposed the Apriori algorithm in 1994 [14]. The algorithm allowed the users to gain valid rules efficiently [15]. The support, confidence, and importance were served as significant indicators in this study to identify association rules. The support denoted the probability of purchasing X and Y simultaneously; confidence the probability of obtaining Y when X is obtained. Assumed the support of "Drug A→Drug B" was 0.30 and the confidence was 0.625. In this case, the probability of Drug A and Drug B occurring jointly in a prescription was 30%; the probability of Drug B being prescribed when Drug A was prescribed was 62.5%. The importance 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" [16].

The followings statement the calculation steps of patients' prescriptions in this study. The operation process was 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 1 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 3 that failed to meet the minimum support.
- Step 5: Repeat the above steps, until the "maximal frequent itemset" so far. Fig. 5 shows the result of drug interactions with the nine patients with different drugs combinations. After the four operations, the DDIs were obtained, which were AB, AC, AE, BC, and BE.



ID	Drug list
1	ABE
2	B
3	BC
4	ABD
5	AC
6	BC
7	AC
8	ABCE
9	ABC

Drug itemset 1	support
A	6
B	7
C	6
D	1
E	2

Drug itemset 2	support
A	6
B	7
C	6
E	2

Drug itemset 3	support
AB	4
AC	4
AE	2
BC	4
BE	2
CE	1

Drug itemset 4	support
AB	4
AC	4
AE	2
BC	4
BE	2

Fig. 5. The example of Apriori algorithm process

3. ANALYSIS RESULTS

The raw data composed of 59 divisions, including the division of pediatrics, the division of general medicine, and the division of cardiovascular surgery. The total number of consultation records is 588,316. The youngest patient is two years old, and the oldest patient is 108 years old, and 51% female and 49% male. The elderly patients are over 30% of the total patients. On the other hand, the general outpatient clinic consultations account for 90.85% of all types of clinical consultations.

Firstly, collect and analyze the severity and incidence rate of drug interactions in all patient consultation records data. For the incidence rate, 21,721 patients have drug interactions; which generates an incidence rate of approximately 4% in all the patients. 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 four out of one hounded patient is on the risks of drug interactions. There are 11753 elderly patients aged 65 and above who have drug interactions. The percentage is 54.1% and p-values < 0.05, which shows significant differences.

For the severity analysis, 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 (0.96) than emergency ones (0.04). Concerning the emergency treatment alone, the division of general medicine shows the highest percentage of 0.966 whereas gynecology shows the lowest with 0.003. In the 25,151 combinations, the proportions of significance grade 1 and grade 2 of drug interactions are 0.288 and 0.711, respectively. The p-value > 0.05, which shows there is no significant difference between genders.

To investing the interaction of drugs with different medical divisions situation, the Pareto analysis was used. Fig. 6 shows the results; cardiovascular surgical proportion reached the highest 16%, family medicine (13.5%), cardiovascular (11.7%), rheumatology and immunology (10.3%) and infectious diseases 8.1%. The result of chi-square test was p-value=0.000, shows there is a significant difference between different medical divisions.

For the elderly patients aged 65 and above, cardiology patients account for the highest proportion of all (0.439). Next to the highest are the percentages of neurology patients (0.143) and cardiovascular surgery patients (0.127). A chi-square test 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 records of aged 65 and above, there are significant differences in drug interactions among the various divisions of medicine.

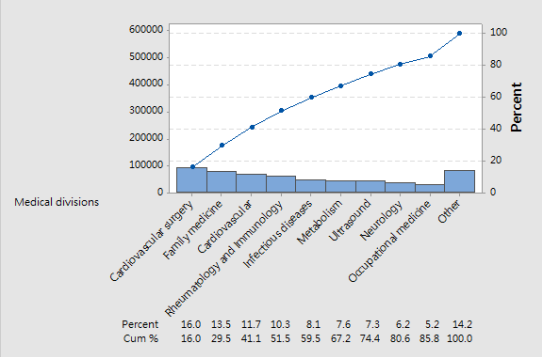


Fig. 6. The Pareto chart of the various medical divisions for DDIs situation

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 of 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 of 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 of 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%).

For the age trend of drug interactions, Fig. 7 showed the results of grade 1 of drug

interactions. The drug interactions are proved to increase with increasing age. From 31-40 years to 61-70 years, the proportion of male patients is higher the percentage of female patients. From 71-80 years, the situation declines as the number of elderly patients varies. Fig. 8 showed the results of grade 2 of drug interactions. Similar to grade 1 of drug interactions, patients increasingly suffer from increasing age from grade 2 of drug interactions at 50 years. The increasing rate of male patients is faster than the female patients. A chi-square test for independence is used to analyze the correlations between age and the incidence rate of drug interactions. The analysis result shows the p-value(=0.000) less than 0.05. Therefore, there is a high correlation between age and incidence rate of drug interactions.

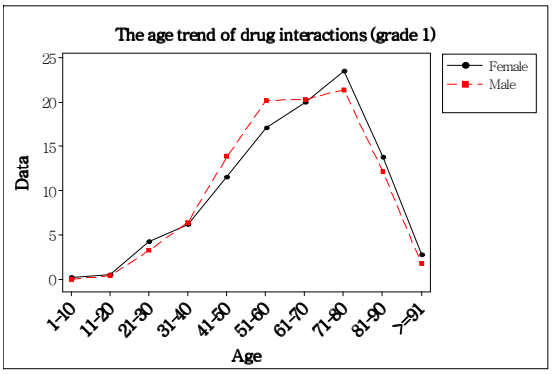


Fig. 7. The age trend of drug interaction for the grade 1

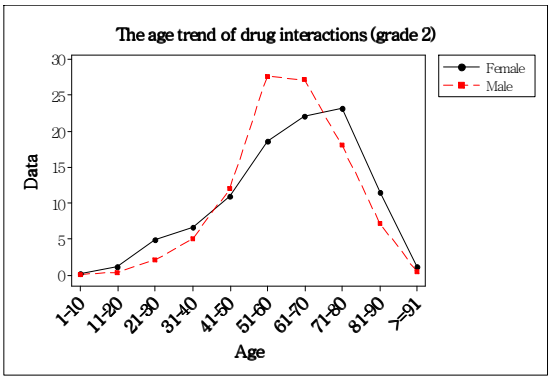


Fig. 8. The age trend of drug interaction for the grade 2

A chi-square test of independence cannot indicate the strength of correlations between patients' age and drug interactions. Therefore, odds ratios were used to conduct a test. The results show that 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).

Further, the association rule mining is used for the patient's 65 years and above. The minimum support set to 10. The confidence level is 80 to eliminate other rules. The analysis results can find two rules 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 of drug interactions due to the combination of these two drugs.

- Result 2: The association rules of Cardiology

  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 of drug interactions due to the combination of these two drugs.

4. DISCUSSION AND CONCLUSION

According to the results of the study, the first five of the grade 1 of drug interactions were Furosemide×Digoxin, Trichlormethiazide× Digoxin, Methotrexate×Sulfasalazine, Digoxin× Indapamide and Digoxin×Hydrochlorothiazide. The Furosemide×Digoxin, Trichlormethiazide× Digoxin, Digoxin× Indapamide and Digoxin× Hydrochlorothiazide will cause disease-suffering arrhythmia. The methotrexate×Sulfasalazine will cause bone marrow suppression and cell anemia. The first five of the grade 2 of drug interactions results as follows. Aspirin*Glimepiride will be the disease had resulted in a reduction in the blood glucose, and promote insulin release. Aspirin×ramipril and Aspirin×perindopril and in clinical practice will lead to instability in a small number of patients with heart disease of heart rate and blood pressure, physicians are advised to reduce disease patient dose of aspirin or is replaced by an alternative drug, propranolol HCl×Propyl-thiouracil in clinic will cause disease suffer from slow heartbeat and hypotension, suggest that doctors should reduce the dose of propranolol HCl. The insulin Human×Aspirin in Mixtard will cause patient stomach discomfort. For patients aged 65 and above of the grade 1 of

drug interactions, Female patients suffering from in digoxin×indapamide is higher than the male, the male disease patients in digoxin× hydrochlorothiazide 152 times is much greater in women's 79 times. On the other hand, the DDIs of the fifth is Spironolactone×ramipril, that the patient potassium concentration increased, leading to potential side effects, such as hands and feet numbness, muscle weakness, serious may result in a drop in blood pressure caused by arrhythmia and death.

Investigating the previous studies found that often failed to make a complete discussion of the differences in drug interactions among older people of different departments and characteristics. Thence, this study explores the association between drug interactions in various departments and prescriptions for patient's 65 years and above. The database of a teaching hospital in north Taiwan is used. After analysis, five conclusions are derived. Firstly, 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. Secondly, 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. Thirdly, as for the incidence rates of grade 1 of drug interactions for the elderly patients are in the different divisions and genders. The highest rates for both female and male patients found in departments of cardiology and cardiovascular surgery, which account for nearly 80% of all cases. Fourthly, 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. Fifthly, 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.

In this paper, the associate rule was used to reveal the severity and the incidence rate of drug interactions in Taiwan Teaching Hospital. The research funding that if data aggregation pretreated through association rules, medical institutions could be informed with useful information for warning system of drug interaction. Moreover, the incidence rate of drug interactions for patients 65 years old higher than other the patients about 2.01 times which indicate that medical institutions should pay attention to the problem of drug interactions among elderly patients. I suggested that the patient should be reminded to describe their medications for medical staffs spontaneously to help doctors for reducing the risk of drug interactions and drug wastage.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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