Evaluation of rational nonsteroidal anti-inflammatory drugs and gastro-protective agents use; association rule data mining using outpatient prescription patterns

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) and gastro-protective agents should be co-prescribed following a standard clinical practice guideline; however, adherence to this guideline in routine practice is unknown. This study applied an association rule model (ARM) to estimate rational NSAIDs and gastro-protective agents use in an outpatient prescriptions dataset.

Methods: A database of hospital outpatients from October 1st, 2013 to September 30th, 2015 was searched for any of the following drugs: oral antacids (A02A), peptic ulcer and gastro-oesophageal reflux disease drugs (GORD, A02B), and anti-inflammatory and anti-rheumatic products, non-steroids or NSAIDs (M01A). Data including patient demographics, diagnoses, and drug utilization were also retrieved. An association rule model was used to analyze co-prescription of the same drug class (i.e., prescriptions within A02A-A02B, M01A) and between drug classes (A02A-A02B & M01A) using the Apriori algorithm in R. The lift value, was calculated by a ratio of confidence to expected confidence, which gave information about the association between drugs in the prescription.

Results: We identified a total of 404,273 patients with 2,575,331 outpatient visits in 2 fiscal years. Mean age was 48 years and 34% were male. Among A02A, A02B and M01A drug classes, 12 rules of associations were discovered with support and confidence thresholds of 1% and 50%. The highest lift was between Omeprazole and Ranitidine (340 visits); about one-third of these visits (118) were prescriptions to non-GORD patients, contrary to guidelines. Another finding was the concomitant use of COX-2 inhibitors (Etoricoxib or Celecoxib) and PPIs. 35.6% of these were for patients aged less than 60 years with no GI complication and no Aspirin, inconsistent with guidelines.

Conclusions: Around one-third of occasions where these medications were co-prescribed were inconsistent with guidelines. With the rapid growth of health datasets, data mining methods may help assess quality of care and concordance with guidelines and best evidence.

Keywords: Data mining, Association rule, Apriori algorithm, Prescription patterns, Rational drug use, Hospital, Data warehouse, Nonsteroidal anti-inflammatory drugs, Gastro-protective agents

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Background
Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and inflammation. However, conventional NSAIDs (e.g., Diclofenac, Meloxicam, Ibuprofen) can induce gastrointestinal (GI) upset and adverse events, especially peptic ulceration [1]. To reduce this risk, gastro-protective agents are commonly co-prescribed with NSAIDs; alternatively, cyclooxygenase (COX)-2 inhibitors (e.g., Etoricoxib, Celecoxib) are used, a new generation of NSAIDs claimed to cause fewer gastrointestinal adverse events [2–4]. Co-prescription of COX-2 inhibitors with gastro-protective agents are recommended only in patients at high risk of GI disease, such as elderly patients (aged ≥ 60 years), those using antiplatelet agents (e.g., Aspirin), or patients with a history of GI events [2, 5].

Commonly used gastro-protective agents are histamine H2-receptor antagonists (H2RAs, e.g., Ranitidine) and proton pump inhibitors (PPIs, e.g., Omeprazole, Pantoprazole, Esomeprazole, Lansoprazole). The H2RAs competitively antagonize the histamine effects at H2-receptors in the stomach to reduce the amount and concentration of gastric acid. PPIS suppress stomach acid secretion by specific inhibition of the H+\textsuperscript{//}K+-ATPase system found at the secretory surface of gastric parietal cells [6–9]. Concomitant use of H2RAs and PPIS are recommended only in the treatment of gastro-oesophageal reflux disease (GORD) [10, 11].

In the past, identification of poor quality drug use in the hospital was not easily done, because of the volume and complexity of prescription data. In our institution (Ramathibodi Hospital, Bangkok, Thailand) data warehouses have been available since 2014, and there has been interest in using these to drive quality improvement in health care practice and service delivery. These data include drug prescriptions, demographic data, diagnoses, laboratory tests, imaging, etc., and are routinely extracted from hospital information systems (HIS).

Currently, a wide variety of data mining algorithms (i.e., technique for big data analysis) are available; they are classified into 2 main categories: supervised and unsupervised learning [12]. Supervised learning algorithms produce a model using classification or regression that can predict the response values for a particular outcome or behavior of interest. Unsupervised learning algorithms describe the form and hidden structure of data, using methods such as clustering, anomaly detection, and association rule mining (ARM), which has been applied for detecting co-prescription patterns in many studies [13–17].

The Apriori algorithm is a classical ARM technique, based on the principle of frequent pattern mining [18–21]. First, a candidate set is generated to identify items that occur with a frequency that exceeds a pre-specified threshold (i.e., defined as the support measure). Second, the association rules are derived by indicating conditional probabilities between a pair of items; groups are defined if the conditional probability value exceeds a user-defined threshold (called the confidence measure).

Our study aimed to assess associations within the gastro-protective agents (H2RAs and PPIS), and NSAIDs (including COX-2 inhibitors), as well as between these two drug classes using ARM. Once associations were identified, prescription patterns were explored for congruence with guidelines.

Methods
An electronic database of outpatients records at Ramathibodi Hospital between October 1st, 2013 and September 30th, 2015 was extracted from the hospital data warehouse focusing on H2RAs and PPIS (A02A and A02B codes), and NSAIDs and COX-2 inhibitors (M01A). Only fields for patient demographics, prescriptions, drug utilization, and diagnoses were retrieved. Two steps of data manipulation and analysis were then performed using R software version 3.3.0 in RStudio\textsuperscript{*} version 0.99.902 (RStudio Inc., Boston, MA, USA). First, the data frame was constructed and then data was analyzed to identify association rules and evaluate rational drug use.

Data retrieval and manipulation
Five tables in the hospital data warehouse were retrieved as follows: 1) physician prescriptions, 2) master drug lists, 3) drug utilization, 4) diagnosis data, and 5) patient demographic data. The study protocol was approved by the ethics committee of Ramathibodi Hospital without requirement of consent for participation. As for our hospital’s rules, data were not available for public and thus we could not provide and share individual patient data.

The physician prescriptions over 2 fiscal years were retrieved. These data had been already cleaned through an “Extract, Transform, Load” (ETL) process while being loaded into the data warehouse on a daily basis [22]. Master drug lists from the data warehouse were also loaded and merged in RStudio\textsuperscript{*}. To manipulate the data frame, R commands were constructed and run to select ambulatory or outpatient prescriptions with Anatomical Therapeutic Chemical (ATC) classification system codes of A02A: Antacids, A02B: Drug for peptic ulcer and GORD, and M01A: Anti-inflammatory and anti-rheumatic products, nonsteroids or NSAIDs (see Table 1).

Two years of data were combined and drug strength and dosage were ascertained from the left 4 digits of the drug code substring, e.g. IBUP1T- (Ibuprofen 200 mg tablet), IBUP2T- (Ibuprofen 400 mg tablet), IBUP-S- (Ibuprofen 100 mg/5 ml) syrup transformed to the same code - IBUP for Ibuprofen. HN (patient’s hospital number) and date were joined to create HNDate, to represent visit date. Data frame was reshaped from long to wide format e.g.
And records with only one drug item per patient per day were excluded.

Drug utilization, diagnosis data, and patients' demographic data were also retrieved from tables in the hospital data warehouse to get each prescription's dose and frequency, primary/secondary diagnosis of each visit (with International Classification of Disease, Tenth Edition ICD-10), date of birth (to calculate age), and gender. All data were merged with physician prescriptions by HNDate.

| Drug code | Name | Drug code | Name |
|-----------|------|-----------|------|
| A02A - Antacids | | M01AA to M01AX, M01AX - conventional NSAIDs |
| ALGY-T- | Alginic acid tablet | ASPT-T- | Acetylsalicylic acid 300 mg |
| ALHY-T- | Aluminium hydroxide 500 mg | ASA1-T | Acetylsalicylic acid 81 mg |
| ALHY-N2 | Aluminium hydroxide 6.10% | CAPN-T- | Acetylsalicylic acid 100 mg |
| ANT-T- | Aluminium hydroxide tablet | CLIR-T- | Sulindac 200 mg |
| ANT-N2 | Aluminium hydroxide 1000 ml | DICF-T- | Diclofenac 25 mg |
| ANT-N1 | Aluminium hydroxide 240 ml | FAFX-T- | Nabumetone 500 mg |
| GAITE-T- | Sodium alginate Dual Action | FLAM-C- | Piroxicam 10 mg |
| GAVI-N- | Sodium alginate Liquid | IBUP-S- | Ibuprofen (100 mg/5 ml) |
| GAST-T- | Bismuth subsalicylate 524 mg | IBUP1T- | Ibuprofen 200 mg |
| MUCT-T- | Rebamipide 100 mg | IBUP2T- | Ibuprofen 400 mg |
| ULCF-N- | Sucralfate 240 ml | INDM-C- | Indomethacin 25 mg |
| ULCF-N1 | Sucralfate 60 ml | MEFN1C- | Mefenamic acid 250 mg |
| ULSN-T- | Sucralfate 500 mg | MEFN2T- | Mefenamic acid 500 mg |
| ULSNT- | Sucralfate 1000 mg | MELO-T- | Meloxicam 7.5 mg |
| A02B - Drug for peptic ulcer and GORD | | MELO1T- | Meloxicam 15 mg |
| CYTT-T- | Misoprostol 200 mcg | NAPS-T- | Naproxen LE 250 mg |
| XAND-T- | Ranitidine 150 mg | NAPX-T- | Naproxen 250 mg |
| COTL2T- | Pantoprazole 20 mg | REMT-T- | Diclofenac 100 mg |
| COTLT- | Pantoprazole 40 mg | VOLS1T- | Diclofenac SR 75 mg |
| DEX1C- | Dextansoprazole 60 mg | VOLS-T- | Diclofenac SR 100 mg |
| DEX1C- | Dextansoprazole 30 mg | M01AH - COX-2 inhibitors |
| LOSC-C | Omeprazole MUPS 20 mg | ARCX4T- | Etoricoxib 30 mg |
| NEXM1T- | Esomeprazole 20 mg | ARCX1T- | Etoricoxib 60 mg |
| NEXM2T- | Esomeprazole 40 mg | ARCX2T- | Etoricoxib 90 mg |
| OMPZ-C | Omeprazole 20 mg | CEL8-C- | Celecoxib 200 mg |
| PARI-T- | Rabeprazole 10 mg | CEL8IC- | Celecoxib 400 mg |
| PARI1T- | Rabeprazole 20 mg | | |
| PRVF1T- | Lansoprazole 15 mg | | |
| PRVF2T- | Lansoprazole 30 mg | | |

Note: every patient in the cohort was prescribed at least one of the listed drugs
Data analysis

Patient age and number of OPD visits/person/year were described using mean (SD) and number of male and number of diagnoses, defined by ICD-10 codes: K20-K29.9, K30-K38.9, K90-K93.8 for gastrointestinal complications. The Apriori algorithm with ARM was applied to assess the pattern of associations within the same drug classes (i.e., gastro-protective agents, NSAIDs) and between different drug classes (i.e., gastro-protective agents and NSAIDs).

Association rules were derived based on prescription data. The rules were aimed to detect prescribing patterns of NSAIDs and gastro-protective agents for individual patients in the same visit with detail as follows: Let \( P \) be a set of prescribed drug items (i.e., NSAIDs and gastro-protective agents) listed in the database and \( P = \{P_1, P_2, \ldots, P_i\} \) be a set of number of prescriptions, where \( P_i \) (1 \( \leq \) i \( \leq \) n) is a set of drugs in prescription \( i \). Given \( X \) and \( Y \) as non-overlapping sets of drug items (i.e., \( X \cap Y = \emptyset \)), the ARM is used to measure how often \( X \) (called antecedent or left-hand-side or LHS) and \( Y \) (called consequent or right-hand-side or RHS) occurred/appeared together in the same prescription \( (P_i) \). The association rules use 3 probability estimations: support, confidence, and lift without adjusting for derivation of multiple sets of drug items. Support is defined as the probability of prescriptions in \( P \) contains \( X \) and \( Y \), i.e., \( \text{support}(X \rightarrow Y) = P(X \cup Y) \). Confidence is defined as the conditional probability of having \( Y \) given \( X \); \( \text{confidence}(X \rightarrow Y) = P(Y|X) \). Lift is the deviation of the support parameter from what would be expected if \( X \) and \( Y \) were independent; \( \text{lift}(X \rightarrow Y) = \frac{P(X,Y)}{P(X) \times P(Y)} \); lift values of <1, >1, and 1 refer to negative, positive, and independent associations between antecedent and consequent, respectively, the larger of the value indicates the more significant of the association. The most significant association was between Omeprazole and Ranitidine with highest lift of 7.6153. The rest was low associations between other drugs and Omeprazole.

Among these 12 association rules, the number of prescriptions of concomitant use for the first and second lifts (i.e., H2RAs and PPIs and COX-2 inhibitors and PPIs) were next calculated. For H2RAs and PPIs (i.e., Ranitidine and Omeprazole), the support and numbers of observations were 0.0552 and 6168, respectively. As a result, 340 (0.0552 \times 6168) observations were prescribed with Omeprazole and Ranitidine on the same day. A total of 128,117 (95.4%) observations were omitted due to prescription of only one drug per visit, leaving 6168 observations for ARM analysis.

The ARM was applied starting with a threshold of 1% for both support and confidence parameters, and increasing the threshold until association rules were found. Twelve rules were identified and pass the thresholds of 1% and 50% for support and confidence parameters, respectively (see Table 2). The strongest support parameter (0.2244) was between Aspirin and Omeprazole. The strongest confidence parameter (0.9738) was between Naproxen and Omeprazole. Lift values of <1, >1, and 1 refer to negative, positive, and independent associations between antecedent and consequent, respectively, the larger of the value indicates the more significant of the association. The most significant association was between Omeprazole and Ranitidine with highest lift of 7.6153. The rest was low associations between other drugs and Omeprazole.

Table 2. LHS, RHS, support, confidence and lift of 12 rules

| Rule no. | LHS | RHS | Support | Confidence | Lift |
|---------|-----|-----|---------|------------|------|
| 1       | OMPZ | XAND | 0.0552  | 0.7944     | 7.6153 |
| 2       | XAND | OMPZ | 0.0552  | 0.5288     | 7.6153 |
| 3       | NAPX | OMPZ | 0.1085  | 0.9738     | 1.4363 |
| 4       | MELD | OMPZ | 0.0315  | 0.9557     | 1.4096 |
| 5       | IBUP | OMPZ | 0.0362  | 0.9028     | 1.3317 |
| 6       | DCF  | OMPZ | 0.0109  | 0.8933     | 1.3177 |
| 7       | ASPT | OMPZ | 0.0399  | 0.8723     | 1.2867 |
| 8       | ASA  | OMPZ | 0.2244  | 0.7840     | 1.1564 |
| 9       | CELB | OMPZ | 0.0483  | 0.7582     | 1.1184 |
| 10      | MOBC | OMPZ | 0.0133  | 0.7522     | 1.1096 |
| 11      | ARCX | OMPZ | 0.0860  | 0.6901     | 1.0179 |
| 12      | ANTC | OMPZ | 0.0315  | 0.5543     | 0.8176 |

From ARM, related data in 3 tables including drug utilization, diagnosis data, and patients’ demographic data, were explored and assessed to evaluate rational use of 2 concomitant drugs. In the first group - concomitant use of H2RAs and PPIs - dose and frequency appearing in each prescription along with clinic data were cross-checked for drug interaction or over-dosage. Number and percentage of prescriptions for any concomitant use of H2RAs and PPIs were compared with GORD (described in primary/secondary diagnosis).

In the second group - concomitant use of COX-2 inhibitors and PPIs - patients’ characteristics, number and percentage of prescriptions by age groups, co-therapy with Aspirin, and GI complication were described.

Results
A total of 2,575,331 outpatient visits over 2 fiscal years were retrieved. The mean age and number of OPD visits were 48.4 (SD = 21.4) years and 4.7 (SD = 4.4) per person per year, respectively, and the majority were females (66%). The percentages with GI complications and arthritis were 1.80% and 0.74%, respectively. Among them, 134,285 prescriptions had at least one oral antacid (A02A), drug for peptic ulcer and GORD (A02B), or NSAIDs (M01A) in the same day. A total of 128,117 (95.4%) observations were omitted due to prescription of only one drug per visit, leaving 6168 observations for ARM analysis.

The ARM was applied starting with a threshold of 1% for both support and confidence parameters, and increasing the threshold until association rules were found. Twelve rules were identified and pass the thresholds of 1% and 50% for support and confidence parameters, respectively (see Table 2). The strongest support parameter (0.2244) was between Aspirin and Omeprazole. The strongest confidence parameter (0.9738) was between Naproxen and Omeprazole. Lift values of <1, >1, and 1 refer to negative, positive, and independent associations between antecedent and consequent, respectively, the larger of the value indicates the more significant of the association. The most significant association was between Omeprazole and Ranitidine with highest lift of 7.6153. The rest was low associations between other drugs and Omeprazole.

Among these 12 association rules, the number of prescriptions of concomitant use for the first and second lifts (i.e., H2RAs and PPIs and COX-2 inhibitors and PPIs) were next calculated. For H2RAs and PPIs (i.e., Ranitidine and Omeprazole), the support and numbers of observations were 0.0552 and 6168, respectively. As a result, 340 (0.0552 \times 6168) visits were prescribed with Omeprazole and Ranitidine on the same day.
drug uses for these 340 visits were therefore explored, see Table 3. Drug dose and frequency from each prescription were retrieved. Among these, one patient was prescribed both drugs from different clinics, 12 patients were prescribed Omeprazole and Ranitidine by the same physicians with taking both drugs at the same meals, while the rest of the patients received two drugs from one physician but for different meals. All GI related diagnoses were further explored among these 340 patients, see Table 4. The results indicate that in 118 visits or one-third of these patients, the combination was not prescribed for GORD.

In the second group, we looked at concomitant use of COX-2 inhibitors with PPIs, a combination that is indicated only in elderly patients or those who have GI complications or are taking Aspirin. From a total of 828 visits, there were no COX-2 inhibitors (i.e., Etoricoxib or Celecoxib) prescribed in the same visit. Of these, 295 (35.6%) visits (Table 5) did not comply with the clinical practice guidelines, i.e. for patients aged less than 60 years with no GI complication and no Aspirin taken.

Discussion
The study applied ARM to find association rules in prescribing drugs that contained any of 2 drug groups in the same day, i.e., NSAIDs and gastro-protective agents. Data were manipulated and analyzed by Apriori algorithm in RStudio®. Twelve rules were found with >1% support and >50% confidence thresholds and revealed 2 non-guideline prescription patterns of NSAIDs and gastro-protective agents from a hospital data warehouse i.e., Omeprazole with Ranitidine, and COX-2 inhibitors with Omeprazole.

The overwhelming majority of prescriptions (95%) were only for single agents, indicating that rational drug prescriptions was occurring the majority of the time. However, the remaining 5% still represented over 6000 prescriptions and these need more analysis to ascertain whether they complied with clinical practice guidelines.

Among scripts with more than one drug, the strongest association was between Omeprazole and Ranitidine, both of which are in the same drug group, (A02B). Although their pharmacological pathways are different [5], most physicians prescribe either one or another. However, evidence from few studies indicated that taking these 2 drugs in the same meal can improve gastric acid control [10, 11].

The second prescription pattern was between COX-2 inhibitors and Omeprazole. There is no cost effectiveness study directly supporting the benefits of this combination strategy [25], and PPIs are clinically not indicated to prescribe with COX-2 inhibitors, except for high GI risk patients [5].

This study showed that ARM could detect possible poor quality of drug prescription patterns from a hospital data warehouse. Applying this ARM in a routine practice of drug prescriptions should support and lead to health care improvement. The ARM has also found benefits in other clinical studies to identify risk patterns for type 2 diabetes [26], analyze the records of patients diagnosed with essential hypertension [27], identify interesting patterns of infection control [28], find disease association rules from the national health insurance research database in Taiwan [29], and to identify product–multiple adverse event associations in the US Vaccine Adverse Event Reporting System (VAERS) [30]. Apriori is an algorithm for generating association rules; other ARM algorithms are Eclat and FP-Growth algorithms [31, 32].

Table 3 Drug's dose and frequency of Omeprazole (OMPZ) and Ranitidine (XAND)

| Code | Dose and frequency | Clinic | Code | Dose and frequency | Clinic |
|------|-------------------|--------|------|-------------------|--------|
| OMPZ | 1 CAP AM SDORP11 | XAND   | 1 TAB BID OFM18 |
| OMPZ | 1 CAP AM SDPMD02 | XAND   | 1 TAB BID SDPMD02 |
| OMPZ | 1 CAP AM OGY111  | XAND   | 1 TAB BID OGY111 |
| OMPZ | 2 CAP AM OPS01   | XAND   | 1 TAB BID OPS01 |
| OMPZ | 1 CAP AM SDOET11 | XAND   | 1 TAB BID SDOET11 |
| OMPZ | 1 CAP AM SDPMD02 | XAND   | 1 TAB BID SDPMD02 |
| OMPZ | 1 CAP BID OPS02  | XAND   | 1 TAB BID OPS02 |
| OMPZ | 1 CAP BID SDPET01| XAND   | 1 TAB BID SDPET01|
| OMPZ | 1 CAP BID OEX01  | XAND   | 1 TAB BID OEX01 |
| OMPZ | 1 CAP BID SDPET01| XAND   | 1 TAB BID SDPET01|
| OMPZ | 1 CAP BID SDOSU05| XAND   | 1 TAB BID SDOSU05|
| OMPZ | 1 CAP BID SDPRP03| XAND   | 2 TAB PM SDPRP03 |
| OMPZ | 2 CAP BID SDPRP03| XAND   | 1 TAB PM SDPRP03 |

CAP capsule, TAB tablet, AM in a morning, PM in an evening, BID twice a day, in morning and evening.
**Table 4** Diagnosis related to GI complications of visits prescribed Omeprazole and Ranitidine on the same day, frequency (%)

| ICD10      | Disease                                                  | N  = 340 |
|------------|----------------------------------------------------------|----------|
| K219       | Gastro-oesophageal reflux disease without oesophagitis   | 221 (65.0) |
| K259       | Gastric ulcer unspecified as acute or chronic, without haemorrhage or perforation | 1 (0.3) |
| K30        | Dyspepsia                                               | 222      |
| K279       | Peptic ulcer, site unspecified Unspecified as acute or chronic, without haemorrhage or perforation | 9 (2.6) |
| K297       | Gastritis, unspecified                                  | 5 (1.5)  |
| K922       | Gastrointestinal haemorrhage, unspecified              | 2 (0.6)  |
| K921       | Melaena                                                | 1 (0.3)  |
| K319       | Disease of stomach and duodenum, unspecified          | 1 (0.3)  |
| K254       | Gastric ulcer Chronic or unspecified with haemorrhage | 1 (0.3)  |
| K210       | Gastro-oesophageal reflux disease with oesophagitis    | 1 (0.3)  |
| K20        | Oesophagitis                                            | 1 (0.3)  |
|            | Non-GORD                                                | 118      |

**Conclusion**

This study used data in a hospital data warehouse to explore the prescription pattern of 2 drug groups. The method uses an existing algorithm (Apriori) within an open source package (R) for deriving the association rules. Twelve rules were found, representing around one-third of visits (i.e., 118 of 340 who were prescribed Omeprazole with Ranitidine and 295 from 828 who were prescribed Omeprazole with Etoricoxib or Celecoxib), where prescriptions were potentially not congruent with guidelines. This Apriori algorithm should be implemented in hospital monitoring systems in order to detect guideline-discordant use of medicines and routinely feedback to prescribers for increased patient safety.

**Table 5** Category of visits prescribed COX-2 inhibitors (Etoricoxib or Celecoxib) with Omeprazole, frequency (%)

| Category                                      | N  = 828 |
|-----------------------------------------------|----------|
| Age (years)                                   |          |
| > = 60                                        | 498 (60.2) |
| 50–59                                         | 233 (28.1) |
| < 40                                          | 97 (11.7)  |
| GI complication (K20-K29.9, K30-K38.9, K90-K93.8) |          |
| Yes                                           | 141 (17.0) |
| No                                            | 687 (83.0) |
| Aspirin taken                                  |          |
| Yes                                           | 11 (1.3)  |
| No                                            | 917 (98.7) |
| Age < 60 years with no GI complication and no Aspirin taken |          |
| Yes                                           | 295 (35.6) |
| No                                            | 533 (64.4) |

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**Availability of data and materials**

As for our hospital’s rule, data were not available for public and thus we could not provide and share individual patient data.

**Authors’ contributions**

OP contributed in conception, acquire and analyze data. AT participated in design and interpret the result. MM and JA participated in discussing the results and revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

**Authors’ information**

Described on the title page.

**Ethics approval and consent to participate**

The study protocol was reviewed and approved by the ethics committee of Ramathibodi Hospital without requirement of consent for participation.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Author details**

1. Momeni M, Katz JD. Mitigating GI risks associated with the use of NSAIDs. Pain Med. 2013;14:518–22.
2. Masclee GMC, Valkhoff VE, Soest EM, Mazzaglia G, Molokhia M, Trifiro G, et al. Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice? Aliment Pharmacol Ther. 2013;38(2):178–89.
3. Satoh H, Amagase K, Takeuchi K. Mucosal protective agents prevent exacerbation of NSAID-induced small intestinal lesions caused by antisecretory drugs in rats. J Pharmacol Exp Ther. 2014;348:227–35.
4. Targownik LE, Thomson PA. Gastroprotective strategies among NSAID users: guidelines for appropriate use in chronic illness. Can Fam Physician. 2006;52:1100–5.
5. Cryer B. A COX-2-specific inhibitor plus a proton-pump inhibitor: is this a reasonable approach to reduction in NSAIDs’ GI toxicity? Am J Gastroenterol. 2006;101:711–3.
6. Huang J, Hunt RH. Pharmacological and pharmacodynamics essentials of H2-receptor antagonists and proton pump inhibitors for the practicing physician. Best Pract Res Clin Gastroenterol. 2001;15(3):355–70.
7. Schubert ML, Peura DA. Reviews in basic and clinical gastroenterology: gastric acid secretion in health and disease. Gastroenterology. 2008;134:1842–60.
8. Laine L, Takeuchi K, Tarnawski. Reviews in basic and clinical gastroenterology: gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology. 2008;135:41–60.
9. Aihara T., Nakamura E., Amagase K., Tomita K., Fujishita T., Furutani K., et al. Pharmacological control of gastric acid secretion for the treatment of acid-related peptic disease: past, present, and future. Pharmacol Therapeut. 2003;98:109–127.

**References**

1. Momeni M, Katz JD. Mitigating GI risks associated with the use of NSAIDs. Pain Med. 2013;14:518–22.
2. Masclee GMC, Valkhoff VE, Soest EM, Mazzaglia G, Molokhia M, Trifiro G, et al. Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice? Aliment Pharmacol Ther. 2013;38(2):178–89.
3. Satoh H, Amagase K, Takeuchi K. Mucosal protective agents prevent exacerbation of NSAID-induced small intestinal lesions caused by antisecretory drugs in rats. J Pharmacol Exp Ther. 2014;348:227–35.
4. Targownik LE, Thomson PA. Gastroprotective strategies among NSAID users: guidelines for appropriate use in chronic illness. Can Fam Physician. 2006;52:1100–5.
5. Cryer B. A COX-2-specific inhibitor plus a proton-pump inhibitor: is this a reasonable approach to reduction in NSAIDs’ GI toxicity? Am J Gastroenterol. 2006;101:711–3.
6. Huang J, Hunt RH. Pharmacological and pharmacodynamics essentials of H2-receptor antagonists and proton pump inhibitors for the practicing physician. Best Pract Res Clin Gastroenterol. 2001;15(3):355–70.
7. Schubert ML, Peura DA. Reviews in basic and clinical gastroenterology: gastric acid secretion in health and disease. Gastroenterology. 2008;134:1842–60.
8. Laine L, Takeuchi K, Tarnawski. Reviews in basic and clinical gastroenterology: gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology. 2008;135:41–60.
9. Aihara T., Nakamura E., Amagase K., Tomita K., Fujishita T., Furutani K., et al. Pharmacological control of gastric acid secretion for the treatment of acid-related peptic disease: past, present, and future. Pharmacol Therapeut. 2003;98:109–127.
10. Abdul-Hussein M, Freeman J, Castell D. Concomitant administration of a histamine 2 receptor antagonist and proton pump inhibitor enhances gastric acid suppression. Pharmacotherapy. 2015;35(12):1124–9.

11. Katz PO, Tutuian R. Histamine receptor antagonists, proton pump inhibitors and their combination in the treatment of gastro-oesophageal reflux disease. Best Pract Res Cl Ga. 2001;15(3):371–84.

12. Han J, Kamber M. Data mining: concepts and techniques. 2nd ed. CA: Morgan Kaufmann Publisher; 2006.

13. Chen TJ, Chou LF, Hwang SJ. Application of a data-mining technique to analyze co-prescription patterns for antacids in Taiwan. Clin Ther. 2003;25:2453–63.

14. He Y, Zheng X, Sit C, Loo WT, Wang ZY, Xie T, et al. Using association rules mining to explore pattern of Chinese medicinal formulas (prescription) in treating and preventing breast cancer recurrence and metastasis. J Transl Med. 2012;10(Suppl 1):S12.

15. Yang D, Kang JH, Park YB, Park YJ, Oh HS, Kim SB. Association rule mining and network analysis in oriental medicine. PLoS One. 2013;8(3):e59241. doi: 10.1371/journal.pone.0059241.

16. Yang PR, Shih WT, Chu YH, Chen PC, Wu CY. Frequency and co-prescription pattern of Chinese herbal products for hypertension in Taiwan: a cohort study. BMC Complement Altern Med. 2015;15:163.

17. Yooosofan A, Ghajar FG, Ayat S, Hamidi S, Mahini F. Identifying association rules among drugs in prescription of a single drugstore using Apriori method. Intell Inf Manag. 2015;7:253–9.

18. Lantz B. Machine learning with R. 2nd ed. Birmingham: Packt Publishing; 2015.

19. Hahsler M, Chelluboina S, Hornik K, Buchta C. The arules R-package ecosystem: analyzing interesting patterns from large transaction data sets. J Mach Learn Res. 2011;12:2021–5.

20. Agrawal R, Imieliński T, Swami A. Mining association rules between sets of items in large databases. In: ACM SIGMOD Record 22(2): 1993: ACM. 1993; 207–16.

21. Agrawal R, Srikant R. Proceedings of the 20th International Conference on Very Large Databases. Fast algorithms for mining association rules in large databases. VLDB. 1994;12:478–99.

22. Reeves L. A manager’s guide to data warehousing. IN: Wiley Publishing; 2009.

23. Hahsler M, Bettena G, Hornik K. Arules - a computational environment for mining association rules and frequent item sets. J Stat Softw. 2005;14(15):1–25.

24. Package ‘arules’. April 14, 2016. Version 1.4–16. URL: https://cran-r-project.org/web/packages/arules/arules.pdf (Accessed 7th Jul 2016).

25. Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling. Health Technol Assess. 2006;10(3):127–64.

26. Ramezanfahani A, Pournik O, Shahraji I, Azad F, Hadaegh F. An application of association rule mining to extract risk pattern for type 2 diabetes using Tehran lipid and glucose study database. Int J Endocrinol Metab. 2015;13(2):25389.

27. Shin A.M., Lee I.H., Lee G.H., Park H.J., Park H.S., Yoon K.I., et.al. Diagnostic analysis of patients with essential hypertension using association rule mining. Healthc Inform Res 2010;16(2):77-81.

28. Brossette S, Sprague AP, Hardin JM, Waiies KB, Jones WT, Moser SA. Association rules and data mining in hospital infection control and public health surveillance. JAMA. 1998;5:373–81.

29. Kuo RJ, Shih CW. Association rule mining through the ant colony system for national health insurance research database in Taiwan. Int J Comput Math. 2007;54:1303–18.

30. Wei L, Scott J. Association rule mining in the US vaccine adverse event reporting system (VAERS). Pharmacoepidemiol Dr S. 2015;24:922–33.

31. Data Mining Algorithms In R. URL: http://en.wikibooks.org/w/index.php?oldid=2579992 (Accessed 11th Apr 2017).

32. Hungyadi D. Performance comparison of Apriori and FP-Growth algorithms in generating association rules. Paris, France: Proceedings of the European Computing Conference; 2011.