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Keywords:	Association Rules, case-crossover design, acute kidney injury, pharmacovigilance, pharmacoepidemiology, older people
Abstract:	Objectives: The aim of this case-crossover study was to apply association rule analysis to ascertain drug combinations contributing to the risk of acute kidney injury (AKI) in adults aged 65 years and older. Method: We sourced a nationwide representative sample of New Zealanders aged ≥65 years from the pharmaceutical collections and hospital discharge information. We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines, diuretics, opioids, non-steroidal anti-inflammatory medications. We extracted the first-time coded diagnosis of AKI from the hospital discharge information. We set up a case-crossover cohort, indexed at the first AKI event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period), and the association of AKI with each frequent drug combination was tested by computing a matched odds-ratio (MOR) and its 95% confidence interval (CI). Results: We identified 55747 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. The frequently used medicines associated with AKI are trimethoprim (MOR=1.68; 95%CI= [1.54-1.80]), ondansetron (MOR=1.43; 95%CI= [1.25-1.64]), codeine phosphate plus metoclopramide (MOR=1.37; 95%CI= [1.11-1.63]), and norfloxacin (MOR=1.24; 95%CI [1.05-1.42]). Conclusion: We applied association rules, a novel methodology, to big data to ascertain drug combinations associated with AKI. Association rules uncovered previously implicated medication classes that increase the risk of AKI in older adults. The finding that ondansetron increases the risk of AKI requires further investigation.

Identifying frequent drug combinations associated with acute kidney injury in older adults using association rules method

Running title: Acute kidney injury in older adults

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Key words: Association Rules; case-crossover design; acute kidney injury; pharmacovigilance; pharmacoepidemiology; older people

Key points:

1. Older adults are at an increased risk of acute kidney injury (AKI) because of aging, multiple comorbidities, and polypharmacy.

2. The association rules method revealed that frequently used drug combinations associated with AKI are trimethoprim, ondansetron, codeine phosphate plus metoclopramide, and norfloxacin.

3. The study has important implications for advancing geriatric pharmacoepidemiology research and medication safety in older people.

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Abstract

Background: Older adults are at an increased risk of AKI because of aging, multiple comorbidities, and polypharmacy.

Objectives: The aim of this case-crossover study was to apply association rule analysis to ascertain drug combinations contributing to the risk of acute kidney injury (AKI) in adults aged 65 years and older.

Method: We sourced a nationwide representative sample of New Zealanders aged ≥65 years from the pharmaceutical collections and hospital discharge information. Prescription records (2005-2015) of drugs of interest were sourced from New Zealand pharmaceutical collections (Pharms). We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines, diuretics, opioids, non-steroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with AKI in older adults. We extracted the first-time coded diagnosis of AKI from the National Minimal Dataset (NMDS). A unique patient identifier linked the prescription dataset to the event dataset, to set up a case-crossover cohort, indexed at the first AKI event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period), and the association of AKI with each frequent drug combination was tested by computing a matched odds-ratio (MOR) and its 95% confidence interval (CI).

Results: We identified 55747 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. Association rules identified several medication classes including antimicrobials, nonsteroidal anti-inflammatory drugs and opioids are associated with AKI. The frequently used medicines associated with AKI are trimethoprim (MOR=1.68; 95%CI= [1.54-1.80]), ondansetron (MOR=1.43; 95%CI= [1.25-1.64]), codeine phosphate plus metoclopramide (MOR=1.37; 95%CI= [1.11-1.63]), and norfloxacin (MOR=1.24; 95%CI [1.05-1.42]).

Conclusion: We applied association rules, a novel methodology, to big data to ascertain drug combinations associated with AKI. Association rules uncovered previously implicated medication classes that increase the risk of AKI in older adults. The finding that ondansetron increases the risk of AKI requires further investigation.

1. Introduction

The association rules (AR) method is regarded as a novel pharmacovigilance tool to investigate frequent medication and medication combinations contributing to adverse drug events (ADEs) (1, 2). AR method is applied widely in pharmacoepidemiological studies to evaluate the complexity of medication combinations and medical comorbidities in older adults, identifying drug interactions and for post-marketing surveillance of vaccine safety (3-5). AR method is also used in the field of bioinformatics to identify transcription factors that control gene transcription (6). This method has also been applied to optimise the selection of clinical pathways in the management of chronic diseases (7). Recent studies have demonstrated the utility of AR in detecting ADEs in older adults. We previously have demonstrated the utility of the AR method to investigate medication patterns associated with fracture risk in older adults (8). To our knowledge, there are no published studies that have applied the AR method specifically investigate medicines contributing to acute kidney injury in older adults.

Acute kidney injury (AKI) is associated with higher morbidity, increased mortality, length of hospital stay and higher hospital costs (9). Older adults are at an increased risk of AKI because of aging, multiple comorbidities, and polypharmacy (10). Medication-induced AKI is a modifiable risk factor, and studies have shown several individual medications can contribute to AKI (11-13). Some of the most common medications associated with AKI include furosemide, metformin, vancomycin and non-steroidal anti-inflammatory drugs (14-16). AKI in older adults is associated with an increased risk of mortality, lower health-related quality of life and increased length of hospital stay (17, 18).A systematic review of the literature concluded that the quality of evidence of medication combinations and their association with the development of AKI is weak (19). In addition, there is limited population-level evidence available on the medication combinations associated with AKI.

In this study, we chose to apply AR method to a case-crossover design as it mitigates confounding from unknown time-invariant confounders. To ensure that a case crossover design will answer our research question we followed all the recommendations stipulated for the application of a case crossover design to our analyses (20). For case crossover designs, the key assumptions are that occurrence of the event must be acute and the exposure must be transient.

The overarching aim of this case-crossover study was to apply the AR method to ascertain patterns of medication combinations contributing to the risk of AKI in older adults aged 65 years and older.

2. Methodology

We obtained ethical approval from the Human Ethics Research Committee, University of Bath (approval number EIRA1-2629).

2.1 Data source

The New Zealand (NZ) Ministry of Health holds national collections of community pharmacy dispensing, hospital discharge details and mortality data details. Pharms is the national collections of all prescription claims made by community pharmacists. It contains prescriptions of medicines funded by the Pharmaceutical Management Agency (PHARMAC). PHARMAC is the New Zealand government agency that decides which pharmaceuticals to publicly fund in New Zealand, and provides funded access to pharmaceuticals for all New Zealanders. The National Minimum Data Set (NMDS) is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients. We have provided a detailed description of both the datasets previously. We used unique encrypted National Health Index (NHI) identifiers to cross-match medication exposure data with hospital events data from NMDS.

2.2 Study subject

We identified from the NMDS all individuals aged 65 years and above with a diagnosis of incident AKI between 01/01/2005 and 31/12/2014. We used the ICD-10-AM (The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) code N17.9 to identify individuals with AKI.

Medication exposure

We were interested to explore the use of medication combinations hence we conducted the analysis at the individual medication level. We chose 178 medicines (**Appendix 1**), funded by PHARMAC, and the prescription durations for these medicines are typically over a short-term, in a duration of fortnights supply. We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines,

diuretics, opioids, non-steroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with AKI (13, 21, 22).

Case- crossover cohort

We created a case-crossover cohort for medication exposures, with two 1-day observation periods and two 5-week (35 days) washout periods, summed up to a 36-day study period. Case-period is the day before the index date. The control period is the period 2-34 days before the index date. We chose a two 5-week washout periods based on our previous study as well as the need to minimise carryover effects and misclassification of medication exposure. We calculated the duration of each prescription by dividing the total dose supplied by the daily dose. Together with the prescription dates, we determined whether an individual had non-intermittent exposure to the medications of interests within the case and control periods. We defined non-intermittent exposure to a medication if the individual was prescribed the medication for more than 80% of the days within the study period. The 80% cut-off is considered as a standard measure for medication-adherence in pharmacoepidemiological studies (i.e. the proportion of days covered ≥ 0.8).

We conducted sensitivity analyses to mitigate medication exposure misclassification. We selected three control periods for each AKI case, defined at -2 to -4 and -8 days. A shorter time window accounted for transient as well as intermittent exposures. The second analyses used case and control periods with a 7-day time window to account for misclassification due to prolonged medication exposures.

The pharmaceutical collections (Pharms) and NMDS data were made available as annual, CSV-formatted datasets, and the above-mentioned filtering and cohort-construction procedures were performed using a computer program written in R (3.4.2, R Core Team, 2016).

2.2 AR methodology and statistical analysis

AR methodology is a data-mining algorithm that extracts from a big dataset frequent and statistically interesting item sets above a chosen frequency threshold. We applied AR in this study to identify drugs and drug combinations that are associated with an increased risk of AKI. In this study, drug combinations including singletons that individuals exposed to with a frequency of at least 1/200 (0.5%) on the day before the event (i.e. within the case-period) are the frequent item sets. For each frequent drug combination, the interestingness statistics are the increased odds of AKI onset due to the exposure.

We expressed the increased odds of AKI onset due to exposures as matched odds-ratio (MOR). From the case-crossover cohort we identified individuals with exposures to medication combinations in the case and the control periods. We counted the number of individuals who were exposed to a medication-combination of interest within the case-period but not the control period (N_1), and within the control-period but not the case-period (N_2). The MOR can then be calculated as N_1/ N_2, and the variance of log (MOR) can be calculated as $(1/ N_1) + (1/ N_2)$.

We used heat maps to display the strength of association between medication exposures and AKI. In the heat map, each row represents an exposure combination, and each column represents a medication that appears at least once in the set of exposure combinations. If a medication appears in a particular exposure combination, the corresponding grid is colored. We then mapped the MOR calculations onto the heat map. The color intensity of each row (i.e. each exposure combination) is proportional to log (MOR) of AKI associated with this combination. The grid bordered with a blue color in the heat map represents log (MOR) > 0 with a confidence level of 95%.

3. Results

We identified 65238 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. Of these, 55,747 had at least one prescription record of the medication of interest (Appendix 2) within the 72-day study period. The distribution of ages was slightly skewed towards the higher age group, and there were more females than males. Majority of them were NZ Europeans, and only a few of them belonged to the Māori ethnic group (Supplementary Table 1). The frequent medication combinations stratified by age groups are shown in Table 1.

Table 1. The frequent medication combination(s) stratified by age groups

Medicine combination (Population)	**65-69** (1856)	**70-74** (7429)	**75-79** (12493)	**80-84** (14150)	**85-89** (12310)	**90 +** (7509)	**Total** (55747)
Amoxycillin + clavulanic acid	75	283	509	578	461	266	2172
Amoxycillin + clavulanic acid + Prednisone	11	54	102	95	66	24	352
Bisacodyl	14	43	83	101	82	67	390
Cetirizine hydrochloride	14	87	177	226	160	105	769

Ciprofloxacin	33	139	204	225	176	110	887
Codeine phosphate	96	481	806	906	769	470	3528
Codeine phosphate + Metoclopramide hydrochloride	10	55	65	78	60	23	291
Codeine phosphate + Prednisone	7	57	99	111	88	38	400
Codeine phosphate + Zopiclone	9	40	70	85	88	56	348
Colchicine	46	167	242	233	151	81	920
Co-trimoxazole	18	128	189	263	230	156	984
Cyclizine hydrochloride	20	69	65	81	64	21	320
Dexamethasone	31	121	155	101	64	27	499
Diazepam	8	71	120	132	111	63	505
Diclofenac sodium	124	310	414	344	221	90	1503
Dihydrocodeine tartrate	28	101	134	136	94	55	548
Domperidone	41	163	254	298	267	176	1199
Doxycycline hydrochloride	11	62	127	117	108	74	499
Erythromycin ethyl succinate	24	62	87	113	101	71	458
Flucloxacillin sodium	20	105	209	227	215	166	942
Glyceryl trinitrate	49	210	424	592	500	293	2068
Haloperidol	13	68	96	122	137	82	518
Hyoscine N-butylbromide	17	62	104	84	61	40	368
Ibuprofen	24	148	261	303	257	154	1147
Loperamide hydrochloride	52	223	325	364	271	138	1373
Loratadine	16	152	255	287	243	185	1138
Lorazepam	8	106	188	248	237	174	961
Metoclopramide hydrochloride	94	344	504	534	419	247	2142
Metoclopramide hydrochloride + Morphine sulphate	19	39	79	86	56	36	315
Miconazole nitrate	4	50	60	89	83	68	354
Morphine hydrochloride	39	103	179	249	194	116	880
Morphine hydrochloride + Morphine sulphate	24	37	70	89	64	22	306
Morphine sulphate	70	264	411	450	345	188	1728
Naproxen	16	90	146	115	78	39	484
Nitrofurantoin	6	59	109	164	164	129	631
Norfloxacin	17	68	118	113	124	95	535
Ondansetron	25	137	213	150	99	46	670
Paracetamol with codeine	50	267	468	551	486	278	2100
Prednisone	119	637	1106	1241	987	493	4583
Prednisone + Zopiclone	14	51	90	113	128	70	466
Prochlorperazine	37	128	182	241	236	138	962
Promethazine hydrochloride	7	46	61	89	111	57	371
Quetiapine	7	76	151	202	226	145	807
Risperidone	10	46	126	180	203	142	707
Roxithromycin	18	111	206	200	210	116	861

Temazepam	16	87	165	214	228	159	869
Triazolam	14	91	192	289	313	204	1103
Trimethoprim	27	156	292	409	513	340	1737
Zopiclone	79	437	810	982	1016	641	3965

Association rules revealed 48 frequently used drug combinations that are associated with AKI (**Figure 1**). AKI is associated commonly with trimethoprim exposure (MOR=1.68; 95%CI= [1.54-1.80]), ondansetron exposure (MOR=1.43; 95%CI= [1.25-1.64]), norfloxacin exposure (MOR=1.24; 95%CI [1.05-1.42]), and concomitant exposures to codeine phosphate and metoclopramide (MOR=1.37; 95%CI= [1.11-1.63]).

Sensitivity analyses

The sensitivity analyses were repeated with (3-day) and weekly (7-day) time-windows. (Supplementary Figure S1 and S2)

3-day time window: Trimethoprim exposure (MOR=1.57; 95%CI= [1.41-1.72), ondansetron exposure (MOR=1.44; 95%CI= [1.25-1.63]).

7-day time window: Trimethoprim exposure (MOR=1.20; 95%CI= [1.01-1.38), ondansetron exposure (MOR=1.49; 95%CI= [1.29-1.68]).

Discussion

In this study, we extended the association rules method to a case-crossover matched cohort of older people to examine medications exposures frequently associated with AKI. AKI is associated with higher mortality, and increasing hospitalisations, and no immediate treatment to reverse AKI exists hence the emphasis remains on identifying and avoiding medicines that are nephrotoxic (23).

Association rules identified several medication classes including antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids increase the risk of AKI. Antimicrobials, ranked in order of increasing MOR, included trimethoprim, co-trimoxazole, norfloxacin, erythromycin, ciprofloxacin, roxithromycin, nitrofurantoin and flucloxacillin. The finding that trimethoprim (MOR=1.68; 95%CI= [1.54-1.80]), poses the highest risk of AKI among the antimicrobial class is supported by evidence from another population-level cohort study

conducted in older adults using the UK primary care database, Clinical Practice Research Datalink (24). This UK study found that trimethoprim (adjusted OR 1.72, 95% CI 1.31 to 2.24) and ciprofloxacin (adjusted OR 1.48, 95% CI 1.03 to 2.13) increased the odds of AKI compared with amoxicillin.

The association rules method also revealed NSAIDs increase the risk of AKI. NSAIDs, ranked in order of increasing MOR, included ibuprofen, diclofenac and naproxen. This finding is consistent with finding from meta-analyses of systematic reviews that showed older people in the general population exposed to non-selective NSAIDs were at higher risk of AKI (OR 2.51, 95%CI 1.52 to 2.68) compared to younger age groups (12).

The finding that morphine increases the risk of AKI in older adults is biologically plausible and congruent with evidence that links opioid use with AKI. The mechanism that opioids may increase the risk of AKI involves complex interaction within the autonomic nervous system, the renin–angiotensin–aldosterone system and anti-diuretic hormone. In addition, dehydration, rhabdomyolysis and urinary retention during opioid exposure can all increase the risk of AKI (25).

The finding that ondansetron increases the risk of AKI requires further investigation. Limited data are available regarding the actual incidence and severity of harm resulting from ondansetron–associated AKI. One study found that co-administration of ondansetron increased cisplatin nephrotoxicity by inhibition of Multiple Toxin and Extrusion Proteins (MATEs) (26). MATEs are excretory proteins found in the proximal tubular cells in humans and facilitate renal excretion of cisplatin. Nephrotoxic potential of co-administration of ondansetron on clearance of drugs via MATE transporters warrants further investigation.

Our study found combinations of codeine phosphate with metoclopramide, zopiclone, prednisone, and the medication combination amoxicillin and clavulanic acid increase the risk of AKI. A systematic review concluded a lack of well-designed studies addressing medication class combination associated with AKI (19). The systematic review found there is only evidence to support the combination of NSAIDs and diuretics with or without additional renin-angiotensin aldosterone agents, contributing to AKI, but the evidence to support other medication combinations with AKI is inadequate.

The sensitivity analyses repeated with (3-day) and weekly (7-day) time-windows did not change the results for trimethoprim and ondansetron. These time windows were chosen to align

with the best practice recommendations for conducting a case-crossover study. The sensitivity analyses confirmed that trimethoprim and ondansetron are associated with AKI in older adults. We did not find effect sizes for codeine phosphate plus metoclopramide and norfloxacin as only fewer individuals in the study cohort were exposed to these medicines.

Strengths

This study exemplifies the role of the association rules method to identify interesting medication combinations across a population linked with AKI. The AR method provides tremendous opportunities for rapidly generating safety data on medicines and their combinations in a real-world population setting and regulatory agencies could benefit from this methodology to monitor for adverse drug events. This study has important implications for pharmacoepidemiology research, and to advance medication safety surveillance in older people invariably underrepresented in clinical trials and current pharmacovigilance tools may be inadequate to uncover important medication combinations contributing to adverse drug events.

Limitations

The use of a case-crossover cohort mitigates confounding from known and measurable confounders such as age, sex, ethnicity and chronic comorbidities. However, we recognise that there is a possibility of confounding by indication due to acute changes in health status, for example, dehydration that may increase the risk of AKI. We mitigated time-varying confounding as we employed a short study duration in our analyses, but residual confounding remains a concern. Our findings are generalisable to older adults but may not be applicable to younger populations who may have different medications and comorbidity patterns. We employed prescriptions claims as a marker of medication use, and we did not confirm medication consumption, overall utilisation was likely to be overestimated. Pharmacy claims data also lack information about self-medication and the use of over-the-counter drugs such as NSAIDs and this can result in medication exposure misclassification. Since our study has identified medication exposures form community pharmacy claims data the findings may not be generalisable to other countries where drug formularies and coverage for drug insurance vary.

In the spirit of following the recommendations and assumptions for implementing a case-crossover design as proposed by Maclure and colleagues (20), we included only transient medication exposures to represent medication exposure during the time at risk of AKI. We

acknowledge this is a strength as a well a methodological limitation trying to fulfill the pre-requisite of transient exposure for implementing a case crossover design, as we were not able to uncover AKI contributed by chronic medication exposures. For example, in a nested case-control study conducted by Huerta et al. an increased risk of AKI was reported with the combination of a diuretic and NSAID (27). We met the assumptions that the outcome of interest must be an acute event and not change over time; AKI is an acute event and is unlikely to change over the short study period employed in our study.

Conclusion: We applied association rules, a novel methodology, to big data to ascertain medication combinations associated with adverse drug events. Association rules uncovered previously implicated medication classes such as antimicrobials, opioids, NSAIDs that increase the risk of AKI in older adults. The finding that ondansetron increases the risk of AKI requires further investigation. In the future, we intend to develop the AR algorithm as Artificial Intelligence technology to predict ADRs occurring and aid clinical decision support to the healthcare provider.

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Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Held F, Le Couteur DG, Blyth FM, Hirani V, Naganathan V, Waite LM, et al. Polypharmacy in older adults: Association Rule and Frequent-Set Analysis to evaluate concomitant medication use. Pharmacological research. 2017;116:39-44.
2. Held FP, Blyth F, Gnjidic D, Hirani V, Naganathan V, Waite LM, et al. Association Rules Analysis of Comorbidity and Multimorbidity: The Concord Health and Aging in Men Project. The journals of gerontology Series A, Biological sciences and medical sciences. 2016;71(5):625-31.

3. Cavallo P, Pagano S, Boccia G, De Caro F, De Santis M, Capunzo M. Network analysis of drug prescriptions. Pharmacoepidemiology and drug safety. 2013;22(2):130-7.
4. Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A, et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. Journal of health services research & policy. 2005;10(4):232-8.
5. Wei L, Scott J. Association rule mining in the US Vaccine Adverse Event Reporting System (VAERS). Pharmacoepidemiology and drug safety. 2015;24(9):922-33.
6. Ceddia G, Martino LN, Parodi A, Secchi P, Campaner S, Masseroli M. Association rule mining to identify transcription factor interactions in genomic regions. Bioinformatics (Oxford, England). 2019.
7. Xia K, Zhong X, Zhang L, Wang J. Optimization of Diagnosis and Treatment of Chronic Diseases Based on Association Analysis Under the Background of Regional Integration. Journal of medical systems. 2019;43(3):46.
8. Nishtala PS, Chyou TY, Held F, Le Couteur DG, Gnjidic D. Association rules method and big data: Evaluating frequent medication combinations associated with fractures in older adults. Pharmacoepidemiology and drug safety. 2018;27(10):1123-30.
9. Kellum JA, Unruh ML, Murugan R. Acute kidney injury. BMJ clinical evidence. 2011;2011.
10. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;65(6):860-9.
11. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ (Clinical research ed). 2013;346:e8525.
12. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC nephrology. 2017;18(1):256.
13. Dorks M, Herget-Rosenthal S, Hoffmann F, Jobski K. Combined use of drugs inhibiting the renin-angiotensin system: prescribing patterns and risk of acute kidney injury in German nursing home residents. Clinical interventions in aging. 2018;13:1035-42.

14. Welch HK, Kellum JA, Kane-Gill SL. Drug-Associated Acute Kidney Injury Identified in the United States Food and Drug Administration Adverse Event Reporting System Database. Pharmacotherapy. 2018;38(8):785-93.
15. Douros A, Bronder E, Klimpel A, Erley C, Garbe E, Kreutz R. Drug-induced kidney injury: A large case series from the Berlin Case-Control Surveillance Study. Clinical nephrology. 2018;89 (2018)(1):18-26.
16. Pai AB, Divine H, Marciniak M, Morreale A, Saseen JJ, Say K, et al. Need for a Judicious Use of Nonsteroidal Anti-inflammatory Drugs to Avoid Community-Acquired Acute Kidney Injury. The Annals of pharmacotherapy. 2019;53(1):95-100.
17. Yokota LG, Sampaio BM, Rocha EP, Balbi AL, Sousa Prado IR, Ponce D. Acute kidney injury in elderly patients: narrative review on incidence, risk factors, and mortality. International journal of nephrology and renovascular disease. 2018;11:217-24.
18. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nature reviews Nephrology. 2017;13(4):241-57.
19. Rivosecchi RM, Kellum JA, Dasta JF, Armahizer MJ, Bolesta S, Buckley MS, et al. Drug Class Combination-Associated Acute Kidney Injury. The Annals of pharmacotherapy. 2016;50(11):953-72.
20. Consiglio GP, Burden AM, Maclure M, McCarthy L, Cadarette SM. Case-crossover study design in pharmacoepidemiology: systematic review and recommendations. Pharmacoepidemiology and drug safety. 2013;22(11):1146-53.
21. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney international. 2015;88(2):396-403.
22. Mizokami F, Mizuno T. Acute kidney injury induced by antimicrobial agents in the elderly: awareness and mitigation strategies. Drugs & aging. 2015;32(1):1-12.
23. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nature reviews Nephrology. 2018;14(10):607-25.
24. Crellin E, Mansfield KE, Leyrat C, Nitsch D, Douglas IJ, Root A, et al. Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. BMJ (Clinical research ed). 2018;360:k341.

25. Mallappallil M, Sabu J, Friedman EA, Salifu M. What Do We Know about Opioids and the Kidney? International journal of molecular sciences. 2017;18(1).

26. Li Q, Guo D, Dong Z, Zhang W, Zhang L, Huang SM, et al. Ondansetron can enhance cisplatin-induced nephrotoxicity via inhibition of multiple toxin and extrusion proteins (MATEs). Toxicology and applied pharmacology. 2013;273(1):100-9.

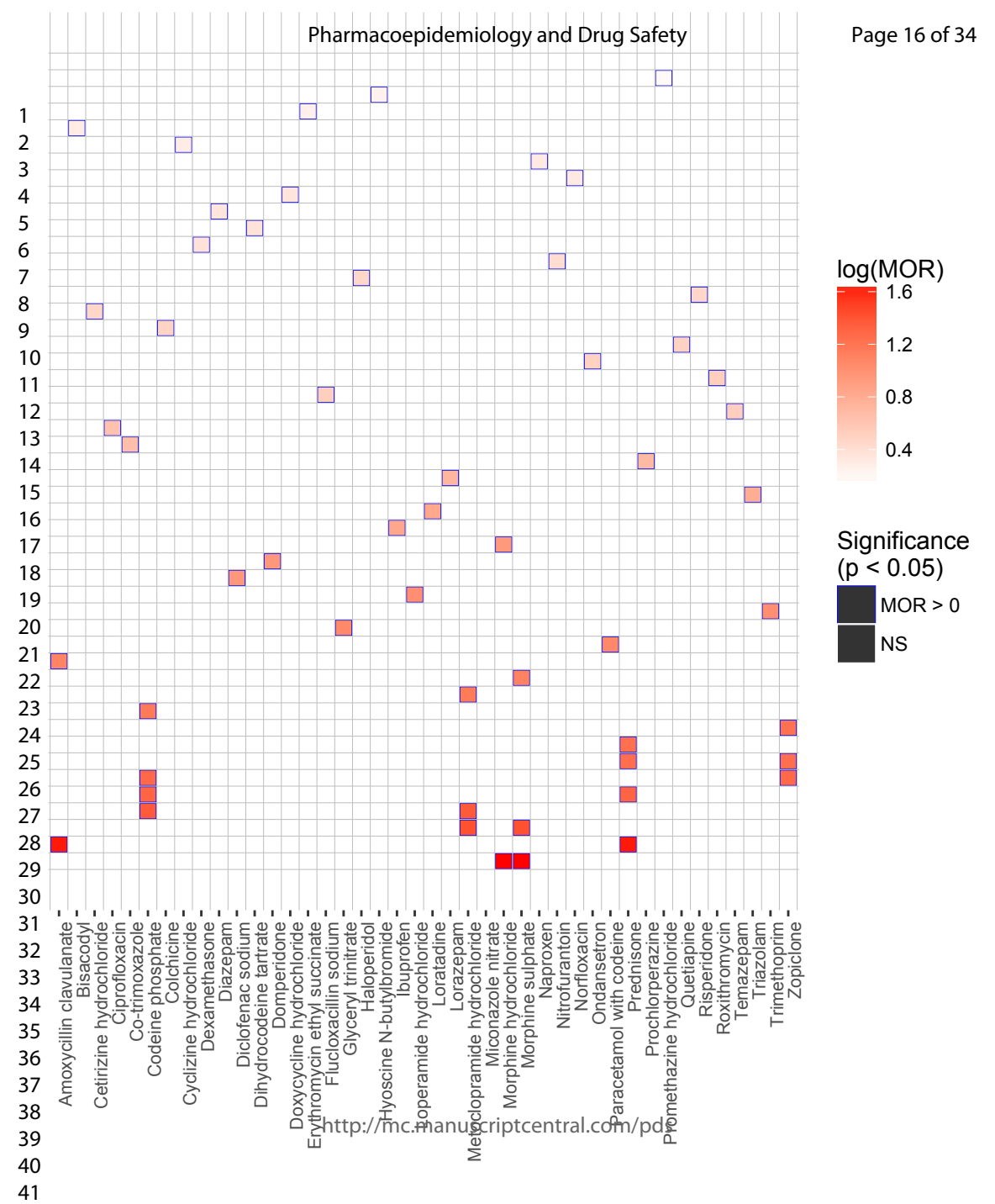
27. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2005;45(3):531-9.

Figures:

Figure 1: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (**one-day time window**) and the statistical significance.

Supplementary Figure S1: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (3-day time window) and the statistical significance.

Supplementary Figure S2: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (7-day time window) and the statistical significance.



~~Predicting~~ Identifying frequent drug combinations associated with acute kidney injury in older adults using association rules method

Running title: Acute kidney injury in older adults

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Key words: Association Rules; case-crossover design; acute kidney injury; pharmacovigilance; pharmacoepidemiology; older people

Key points:

1. Older adults are at an increased risk of acute kidney injury (AKI) because of aging, multiple comorbidities, and polypharmacy.

2. The association rules method revealed that frequently used drug combinations associated with AKI are trimethoprim, ondansetron, codeine phosphate plus metoclopramide, and norfloxacin.

3. The study has important implications for advancing geriatric pharmacoepidemiology research and medication safety in older people.

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Abstract

Background: Older adults are at an increased risk of AKI because of aging, multiple comorbidities, and polypharmacy.

Objectives: The aim of this case-crossover study was to apply association rule analysis to ascertain drug combinations contributing to the risk of acute kidney injury (AKI) in adults aged 65 years and older.

Method: We sourced a nationwide representative sample of New Zealanders aged ≥65 years from the pharmaceutical collections and hospital discharge information. Prescription records (2005-2015) of drugs of interest were sourced from New Zealand pharmaceutical collections (Pharms). We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines, diuretics, opioids, non-steroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with AKI in older adults. We extracted the first-time coded diagnosis of AKI from the National Minimal Dataset (NMDS). A unique patient identifier linked the prescription dataset to the event dataset, to set up a case-crossover cohort, indexed at the first AKI event. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with a 35-day washout period), and the association of AKI with each frequent drug combination was tested by computing a matched odds-ratio (MOR) and its 95% confidence interval (CI).

Results: We identified 55747 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. Association rules identified several medication classes including antimicrobials, nonsteroidal anti-inflammatory drugs and opioids are associated with AKI. The frequently used medicines associated with AKI are trimethoprim (MOR=1.68; 95%CI= [1.54-1.80]), ondansetron (MOR=1.43; 95%CI= [1.25-1.64]), codeine phosphate plus metoclopramide (MOR=1.37; 95%CI= [1.11-1.63]), and norfloxacin (MOR=1.24; 95%CI [1.05-1.42]).

Conclusion: We applied association rules, a novel methodology, to big data to ascertain drug combinations associated with AKI. Association rules uncovered previously implicated medication classes that increase the risk of AKI in older adults. The finding that ondansetron increases the risk of AKI requires further investigation.

1. Introduction

The association rules (AR) method is regarded as a novel pharmacovigilance tool to investigate frequent medication and medication combinations contributing to adverse drug events (ADEs) (1, 2). AR method is applied widely in pharmacoepidemiological studies to evaluate the complexity of medication combinations and medical comorbidities in older adults, identifying drug interactions and for post-marketing surveillance of vaccine safety (3-5). AR method is also used in the field of bioinformatics to identify transcription factors that control gene transcription (6). This method has also been applied to optimise the selection of clinical pathways in the management of chronic diseases (7). Recent studies have demonstrated the utility of AR in detecting ADEs in older adults. We previously have demonstrated the utility of the AR method to investigate medication patterns associated with fracture risk in older adults (8). To our knowledge, there are no published studies that have applied the AR method specifically investigate medicines contributing to acute kidney injury in older adults.

Acute kidney injury (AKI) is associated with higher morbidity, increased mortality, length of hospital stay and higher hospital costs (9). Older adults are at an increased risk of AKI because of aging, multiple comorbidities, and polypharmacy (10). Medication-induced AKI is a modifiable risk factor, and studies have shown several individual medications can contribute to AKI (11-13). Some of the most common medications associated with AKI include furosemide, metformin, vancomycin and non-steroidal anti-inflammatory drugs (14-16). AKI in older adults is associated with an increased risk of mortality, lower health-related quality of life and increased length of hospital stay (17, 18).A systematic review of the literature concluded that the quality of evidence of medication combinations and their association with the development of AKI is weak (19). In addition, there is limited population-level evidence available on the medication combinations associated with AKI.

In this study, we chose to apply AR method to a case-crossover design as it mitigates confounding from unknown time-invariant confounders. To ensure that a case crossover design will answer our research question we followed all the recommendations stipulated for the application of a case crossover design to our analyses (20). For case crossover designs, the key assumptions are that occurrence of the event must be acute and the exposure must be transient.

The overarching aim of this case-crossover study was to apply the AR method to ascertain patterns of medication combinations contributing to the risk of AKI in older adults aged 65 years and older.

2. Methodology

We obtained ethical approval from the Human Ethics Research Committee, University of Bath (approval number EIRA1-2629).

2.1 Data source

The New Zealand (NZ) Ministry of Health holds national collections of community pharmacy dispensing, hospital discharge details and mortality data details. Pharms is the national collections of all prescription claims made by community pharmacists. It contains prescriptions of medicines funded by the Pharmaceutical Management Agency (PHARMAC). PHARMAC is the New Zealand government agency that decides which pharmaceuticals to publicly fund in New Zealand, and provides funded access to pharmaceuticals for all New Zealanders. The National Minimum Data Set (NMDS) is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients. We have provided a detailed description of both the datasets previously. We used unique encrypted National Health Index (NHI) identifiers to cross-match medication exposure data with hospital events data from NMDS.

2.2 Study subject

We identified from the NMDS all individuals aged 65 years and above with a diagnosis of incident AKI between 01/01/2005 and 31/12/2014. We used the ICD-10-AM (The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) code N17.9 to identify individuals with AKI.

Medication exposure

We were interested to explore the use of medication combinations hence we conducted the analysis at the individual medication level. We chose 178 medicines (**Appendix 1**), funded by PHARMAC, and the prescription durations for these medicines are typically over a short-term, in a duration of fortnights supply. We classified medication exposure, as a binary variable, at individual drug level belonging to medication classes including antimicrobials, antihistamines,

diuretics, opioids, non-steroidal anti-inflammatory medications. Several studies have associated the drugs of interest from these medication classes with AKI (13, 21, 22).

Case- crossover cohort

We created a case-crossover cohort for medication exposures, with two 1-day observation periods and two 5-week (35 days) washout periods, summed up to a 36-day study period~~(Figure 1)~~. Case-period is the day before the index date. The control period is the period 2-34 days before the index date. We chose a two 5-week washout periods based on our previous study as well as the need to minimise carryover effects and misclassification of medication exposure. We calculated the duration of each prescription by dividing the total dose supplied by the daily dose. Together with the prescription dates, we determined whether an individual had non-intermittent exposure to the medications of interests within the case and control periods. We defined non-intermittent exposure to a medication if the individual was prescribed the medication for more than 80% of the days within the study period. The 80% cut-off is considered as a standard measure for medication-adherence in pharmacoepidemiological studies (i.e. the proportion of days covered ≥ 0.8).

We conducted sensitivity analyses to mitigate medication exposure misclassification. We selected three control periods for each AKI case, defined at -2 to -4 and -8 days. A shorter time window accounted for transient as well as intermittent exposures. The second analyses used case and control periods with a 7-day time window to account for misclassification due to prolonged medication exposures.

The pharmaceutical collections (Pharms) and NMDS data were made available as annual, CSV-formatted datasets, and the above-mentioned filtering and cohort-construction procedures were performed using a computer program written in R (3.4.2, R Core Team, 2016).

2.2 AR methodology and statistical analysis

AR methodology is a data-mining algorithm that extracts from a big dataset frequent and statistically interesting item sets above a chosen frequency threshold. We applied AR in this study to identify drugs and drug combinations that are associated with an increased risk of AKI. In this study, drug combinations including singletons that individuals exposed to with a frequency of at least 1/200 (0.5%) on the day before the event (i.e. within the case-period) are the frequent item sets. For each frequent drug combination, the interestingness statistics are the increased odds of AKI onset due to the exposure.

We expressed the increased odds of AKI onset due to exposures as matched odds-ratio (MOR). From the case-crossover cohort we identified individuals with exposures to medication combinations in the case and the control periods. We counted the number of individuals who were exposed to a medication-combination of interest within the case-period but not the control period (N_1), and within the control-period but not the case-period (N_2). The MOR can then be calculated as N_1/ N_2, and the variance of log (MOR) can be calculated as $(1/ N_1) + (1/ N_2)$.

We used heat maps to display the strength of association between medication exposures and AKI. In the heat map, each row represents an exposure combination, and each column represents a medication that appears at least once in the set of exposure combinations. If a medication appears in a particular exposure combination, the corresponding grid is colored. We then mapped the MOR calculations onto the heat map. The color intensity of each row (i.e. each exposure combination) is proportional to log (MOR) of AKI associated with this combination. The grid bordered with a blue color in the heat map represents log (MOR) > 0 with a confidence level of 95%.

3. Results

We identified 65238 individuals (mean age 82.14) from 2005 to 2014 with incident AKI and exposed to at least one of the drugs of interest. Of these, 55,747 had at least one prescription record of the medication of interest (Appendix 2) within the 72-day study period. The distribution of ages was slightly skewed towards the higher age group, and there were more females than males. Majority of them were NZ Europeans, and only a few of them belonged to the Māori ethnic group (Supplementary Table 1). The frequent medication combinations stratified by age groups are shown in Table 1.

Table 1. The frequent medication combination(s) stratified by age groups

Medicine combination (Population)	65-69 (1856)	70-74 (7429)	75-79 (12493)	80-84 (14150)	85-89 (12310)	90 + (7509)	Total (55747)
Amoxycillin + clavulanic acid	75	283	509	578	461	266	2172
Amoxycillin + clavulanic acid + Prednisone	11	54	102	95	66	24	352
Bisacodyl	14	43	83	101	82	67	390
Cetirizine hydrochloride	14	87	177	226	160	105	769

Ciprofloxacin	33	139	204	225	176	110	887
Codeine phosphate	96	481	806	906	769	470	3528
Codeine phosphate + Metoclopramide hydrochloride	10	55	65	78	60	23	291
Codeine phosphate + Prednisone	7	57	99	111	88	38	400
Codeine phosphate + Zopiclone	9	40	70	85	88	56	348
Colchicine	46	167	242	233	151	81	920
Co-trimoxazole	18	128	189	263	230	156	984
Cyclizine hydrochloride	20	69	65	81	64	21	320
Dexamethasone	31	121	155	101	64	27	499
Diazepam	8	71	120	132	111	63	505
Diclofenac sodium	124	310	414	344	221	90	1503
Dihydrocodeine tartrate	28	101	134	136	94	55	548
Domperidone	41	163	254	298	267	176	1199
Doxycycline hydrochloride	11	62	127	117	108	74	499
Erythromycin ethyl succinate	24	62	87	113	101	71	458
Flucloxacillin sodium	20	105	209	227	215	166	942
Glyceryl trinitrate	49	210	424	592	500	293	2068
Haloperidol	13	68	96	122	137	82	518
Hyoscine N-butylbromide	17	62	104	84	61	40	368
Ibuprofen	24	148	261	303	257	154	1147
Loperamide hydrochloride	52	223	325	364	271	138	1373
Loratadine	16	152	255	287	243	185	1138
Lorazepam	8	106	188	248	237	174	961
Metoclopramide hydrochloride	94	344	504	534	419	247	2142
Metoclopramide hydrochloride + Morphine sulphate	19	39	79	86	56	36	315
Miconazole nitrate	4	50	60	89	83	68	354
Morphine hydrochloride	39	103	179	249	194	116	880
Morphine hydrochloride + Morphine sulphate	24	37	70	89	64	22	306
Morphine sulphate	70	264	411	450	345	188	1728
Naproxen	16	90	146	115	78	39	484
Nitrofurantoin	6	59	109	164	164	129	631
Norfloxacin	17	68	118	113	124	95	535
Ondansetron	25	137	213	150	99	46	670
Paracetamol with codeine	50	267	468	551	486	278	2100
Prednisone	119	637	1106	1241	987	493	4583
Prednisone + Zopiclone	14	51	90	113	128	70	466
Prochlorperazine	37	128	182	241	236	138	962
Promethazine hydrochloride	7	46	61	89	111	57	371
Quetiapine	7	76	151	202	226	145	807
Risperidone	10	46	126	180	203	142	707
Roxithromycin	18	111	206	200	210	116	861

Temazepam	16	87	165	214	228	159	869
Triazolam	14	91	192	289	313	204	1103
Trimethoprim	27	156	292	409	513	340	1737
Zopiclone	79	437	810	982	1016	641	3965

Table 1: Characteristics of the study cohort stratified by age groups.

	65-69 years (n = 1856)	70-74 years (n = 7429)	75-79 years (n = 12493)	80-84 years (n = 14150)	85-89 years (n = 12310)	90+ years (n = 7509)
Asian	48	235	408	353	239	120
MELAA	5	15	33	39	30	12
Māori	363	1109	1231	809	317	119
NZ-European	1217	5358	9749	12057	11096	6907
Other	54	206	371	432	377	266
Pacific	169	506	701	460	251	85
Female	739	3017	5236	6604	6375	4522
Male	1117	4412	7257	7546	5935	2987

Association rules revealed 48 frequently used drug combinations that are associated with AKI (**Figure 12**). AKI is associated commonly with trimethoprim exposure (MOR=1.68; 95%CI= [1.54-1.80]), ondansetron exposure (MOR=1.43; 95%CI= [1.25-1.64]), norfloxacin exposure (MOR=1.24; 95%CI [1.05-1.42]), and concomitant exposures to codeine phosphate and metoclopramide (MOR=1.37; 95%CI= [1.11-1.63]).

Sensitivity analyses

The sensitivity analyses were repeated with (3-day) and weekly (7-day) time-windows. (Supplementary Figure S1 and S2)

3-day time window: Trimethoprim exposure (MOR=1.57; 95%CI= [1.41-1.72), ondansetron exposure (MOR=1.44; 95%CI= [1.25-1.63]).

7-day time window: Trimethoprim exposure (MOR=1.20; 95%CI= [1.01-1.38), ondansetron exposure (MOR=1.49; 95%CI= [1.29-1.68]).

Discussion

In this study, we extended the association rules method to a case-crossover matched cohort of older people to examine medications exposures frequently associated with AKI. AKI is associated with higher mortality, and increasing hospitalisations, and no immediate treatment to reverse AKI exists hence the emphasis remains on identifying and avoiding medicines that are nephrotoxic (23).

Association rules identified several medication classes including antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids increase the risk of AKI. Antimicrobials, ranked in order of increasing MOR, included trimethoprim, co-trimoxazole, norfloxacin, erythromycin, ciprofloxacin, roxithromycin, nitrofurantoin and flucloxacillin. The finding that trimethoprim (MOR=1.68; 95%CI= [1.54-1.80]), poses the highest risk of AKI among the antimicrobial class is supported by evidence from another population-level cohort study conducted in older adults using the UK primary care database, Clinical Practice Research Datalink (24). This UK study found that trimethoprim (adjusted OR 1.72, 95% CI 1.31 to 2.24) and ciprofloxacin (adjusted OR 1.48, 95% CI 1.03 to 2.13) increased the odds of AKI compared with amoxicillin.

The association rules method also revealed NSAIDs increase the risk of AKI. NSAIDs, ranked in order of increasing MOR, included ibuprofen, diclofenac and naproxen. This finding is consistent with finding from meta-analyses of systematic reviews that showed older people in the general population exposed to non-selective NSAIDs were at higher risk of AKI (OR 2.51, 95%CI 1.52 to 2.68) compared to younger age groups (12).

The finding that morphine increases the risk of AKI in older adults is biologically plausible and congruent with evidence that links opioid use with AKI. The mechanism that opioids may increase the risk of AKI involves complex interaction within the autonomic nervous system, the renin–angiotensin–aldosterone system and anti-diuretic hormone. In addition, dehydration, rhabdomyolysis and urinary retention during opioid exposure can all increase the risk of AKI (25).

The finding that ondansetron increases the risk of AKI requires further investigation. Limited data are available regarding the actual incidence and severity of harm resulting from ondansetron–associated AKI. One study found that co-administration of ondansetron increased cisplatin nephrotoxicity by inhibition of Multiple Toxin and Extrusion Proteins (MATEs) (26). MATEs are excretory proteins found in the proximal tubular cells in humans and facilitate renal excretion of cisplatin. Nephrotoxic potential of co-administration of ondansetron on clearance of drugs via MATE transporters warrants further investigation.

Our study found combinations of codeine phosphate with metoclopramide, zopiclone, prednisone, and the medication combination amoxicillin and clavulanic acid increase the risk of AKI. A systematic review concluded a lack of well-designed studies addressing medication class combination associated with AKI (19). The systematic review found there is only evidence to support the combination of NSAIDs and diuretics with or without additional renin-angiotensin aldosterone agents, contributing to AKI, but the evidence to support other medication combinations with AKI is inadequate.

The sensitivity analyses repeated with (3-day) and weekly (7-day) time-windows did not change the ~~overall~~ results for trimethoprim and ondansetron. These time windows were chosen to align with the best practice recommendations for conducting a case-crossover study. The sensitivity analyses confirmed that trimethoprim and~~,~~ ondansetron~~, codeine phosphate plus metoclopramide, and norfloxacin~~ are associated with AKI in older adults. We did not find effect sizes for codeine phosphate plus metoclopramide and norfloxacin as only fewer individuals in the study cohort were exposed to these medicines.

Strengths

This study exemplifies the role of the association rules method to identify interesting medication combinations across a population linked with AKI. The AR method provides tremendous opportunities for rapidly generating safety data on medicines and their combinations in a real-world population setting and regulatory agencies could benefit from this methodology to monitor for adverse drug events. This study has important implications for pharmacoepidemiology research, and to advance medication safety surveillance in older people invariably underrepresented in clinical trials and current pharmacovigilance tools may be inadequate to uncover important medication combinations contributing to adverse drug events.

Limitations

The use of a case-crossover cohort mitigates confounding from known and measurable confounders such as age, sex, ethnicity and chronic comorbidities. However, we recognise that there is a possibility of confounding by indication due to acute changes in health status, for example, dehydration that may increase the risk of AKI. We mitigated time-varying confounding as we employed a short study duration in our analyses, but residual confounding remains a concern. Our findings are generalisable ~~as we applied the AR method to the national population of~~ to older adults but may not be applicable to younger populations who may have different medications and comorbidity patterns. ~~However,~~ W~~w~~e employed prescriptions claims as a marker of medication use, and we did not confirm medication consumption, overall utilisation was likely to be overestimated. Pharmacy claims data also lack information about self-medication and the use of over-the-counter drugs such as NSAIDs and this can result in medication exposure misclassification. Since our study has identified medication exposures form community pharmacy claims data the findings may not be generalisable to other countries where drug formularies and coverage for drug insurance vary.

In the spirit of following the recommendations and assumptions for implementing a case-crossover design as proposed by Maclure and colleagues (20), we included only transient medication exposures to represent medication exposure during the time at risk of AKI. We acknowledge this is a strength as a well a methodological limitation trying to fulfill the pre-requisite of transient exposure for implementing a case crossover design, as we were not able to uncover AKI contributed by chronic medication exposures. For example, in a nested case-control study conducted by Huerta et al. an increased risk of AKI was reported with the combination of a diuretic and NSAID (27). We met the assumptions that the outcome of interest must be an acute event and not change over time; AKI is an acute event and is unlikely to change over the short study period employed in our study.

Conclusion: We applied association rules, a novel methodology, to big data to ascertain medication combinations associated with adverse drug events. Association rules uncovered previously implicated medication classes such as antimicrobials, opioids, NSAIDs that increase the risk of AKI in older adults. The finding that ondansetron increases the risk of AKI requires further investigation. In the future, we intend to develop the AR algorithm as Artificial Intelligence technology to predict ADRs occurring and aid clinical decision support to the healthcare provider.

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Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Held F, Le Couteur DG, Blyth FM, Hirani V, Naganathan V, Waite LM, et al. Polypharmacy in older adults: Association Rule and Frequent-Set Analysis to evaluate concomitant medication use. Pharmacological research. 2017;116:39-44.
2. Held FP, Blyth F, Gnjidic D, Hirani V, Naganathan V, Waite LM, et al. Association Rules Analysis of Comorbidity and Multimorbidity: The Concord Health and Aging in Men Project. The journals of gerontology Series A, Biological sciences and medical sciences. 2016;71(5):625-31.
3. Cavallo P, Pagano S, Boccia G, De Caro F, De Santis M, Capunzo M. Network analysis of drug prescriptions. Pharmacoepidemiology and drug safety. 2013;22(2):130-7.
4. Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A, et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. Journal of health services research & policy. 2005;10(4):232-8.
5. Wei L, Scott J. Association rule mining in the US Vaccine Adverse Event Reporting System (VAERS). Pharmacoepidemiology and drug safety. 2015;24(9):922-33.
6. Ceddia G, Martino LN, Parodi A, Secchi P, Campaner S, Masseroli M. Association rule mining to identify transcription factor interactions in genomic regions. Bioinformatics (Oxford, England). 2019.
7. Xia K, Zhong X, Zhang L, Wang J. Optimization of Diagnosis and Treatment of Chronic Diseases Based on Association Analysis Under the Background of Regional Integration. Journal of medical systems. 2019;43(3):46.
8. Nishtala PS, Chyou TY, Held F, Le Couteur DG, Gnjidic D. Association rules method and big data: Evaluating frequent medication combinations associated with fractures in older adults. Pharmacoepidemiology and drug safety. 2018;27(10):1123-30.

9. Kellum JA, Unruh ML, Murugan R. Acute kidney injury. BMJ clinical evidence. 2011;2011.
10. Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2015;65(6):860-9.
11. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ (Clinical research ed). 2013;346:e8525.
12. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC nephrology. 2017;18(1):256.
13. Dorks M, Herget-Rosenthal S, Hoffmann F, Jobski K. Combined use of drugs inhibiting the renin-angiotensin system: prescribing patterns and risk of acute kidney injury in German nursing home residents. Clinical interventions in aging. 2018;13:1035-42.
14. Welch HK, Kellum JA, Kane-Gill SL. Drug-Associated Acute Kidney Injury Identified in the United States Food and Drug Administration Adverse Event Reporting System Database. Pharmacotherapy. 2018;38(8):785-93.
15. Douros A, Bronder E, Klimpel A, Erley C, Garbe E, Kreutz R. Drug-induced kidney injury: A large case series from the Berlin Case-Control Surveillance Study. Clinical nephrology. 2018;89 (2018)(1):18-26.
16. Pai AB, Divine H, Marciniak M, Morreale A, Saseen JJ, Say K, et al. Need for a Judicious Use of Nonsteroidal Anti-inflammatory Drugs to Avoid Community-Acquired Acute Kidney Injury. The Annals of pharmacotherapy. 2019;53(1):95-100.
17. Yokota LG, Sampaio BM, Rocha EP, Balbi AL, Sousa Prado IR, Ponce D. Acute kidney injury in elderly patients: narrative review on incidence, risk factors, and mortality. International journal of nephrology and renovascular disease. 2018;11:217-24.
18. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nature reviews Nephrology. 2017;13(4):241-57.

19. Rivosecchi RM, Kellum JA, Dasta JF, Armahizer MJ, Bolesta S, Buckley MS, et al. Drug Class Combination-Associated Acute Kidney Injury. The Annals of pharmacotherapy. 2016;50(11):953-72.
20. Consiglio GP, Burden AM, Maclure M, McCarthy L, Cadarette SM. Case-crossover study design in pharmacoepidemiology: systematic review and recommendations. Pharmacoepidemiology and drug safety. 2013;22(11):1146-53.
21. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney international. 2015;88(2):396-403.
22. Mizokami F, Mizuno T. Acute kidney injury induced by antimicrobial agents in the elderly: awareness and mitigation strategies. Drugs & aging. 2015;32(1):1-12.
23. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nature reviews Nephrology. 2018;14(10):607-25.
24. Crellin E, Mansfield KE, Leyrat C, Nitsch D, Douglas IJ, Root A, et al. Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. BMJ (Clinical research ed). 2018;360:k341.
25. Mallappallil M, Sabu J, Friedman EA, Salifu M. What Do We Know about Opioids and the Kidney? International journal of molecular sciences. 2017;18(1).
26. Li Q, Guo D, Dong Z, Zhang W, Zhang L, Huang SM, et al. Ondansetron can enhance cisplatin-induced nephrotoxicity via inhibition of multiple toxin and extrusion proteins (MATEs). Toxicology and applied pharmacology. 2013;273(1):100-9.
27. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2005;45(3):531-9.

Figures:

~~**Figure 1:** Schematic diagram of the case-crossover cohort.~~

Figure 12: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (**one-day time window**) and the statistical significance.

Supplementary Figure S1: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (3-day time window) and the statistical significance.

Supplementary Figure S2: Heat map showing medication-exposure combinations and the MOR of AKI due to case-period exposures (7-day time window) and the statistical significance.

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CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

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