Medicine-Induced Acute Kidney Injury Findings from Spontaneous Reporting Systems, Sequence Symmetry Analysis and a Case–Control Study with a Focus on Medicines Used in Primary Care

Elizabeth E. Roughead1 · Mhairi Kerr1 · Anna Moffat1 · Gizat M. Kassie1 · Nicole Pratt1

Abstract

Introduction   Primary care provides an opportunity to prevent community acquired, medicine or drug-induced acute kidney injury. One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a list of nephrotoxic medicines that are most problematic in primary care, particularly one that provides a comparison of risks across medicines.

Objective   The aim of this study was to consolidate evidence on the risks associated with medicines and acute kidney injury, with a focus on medicines used in primary care.

Method   We searched the MEDLINE and EMBASE databases to identify published studies of all medicines associated with acute kidney injury identified from spontaneous report data. For each medicine positively associated with acute kidney injury, as identified from spontaneous reports, we implemented a sequence symmetry analysis (SSA) and a case–control design to determine the association between the medicine and hospital admission with a primary diagnosis of acute kidney injury (representing community-acquired acute kidney injury). Administrative claims data held by the Australian Government Department of Veterans’ Affairs for the study period 2005–2019 were used.

Results   We identified 89 medicines suspected of causing acute kidney injury based on spontaneous report data and a reporting odds ratio above 2, from Japan, France and the US. Spironolactone had risk estimates of 3 or more based on spontaneous reports, SSA and case–control methods, while furosemide and trimethoprim with sulfamethoxazole had risk estimates of 1.5 or more. Positive association with SSA and spontaneous reports, but not case control, showed zoledronic acid had risk estimates above 2, while candesartan telmisartan, simvastatin, naproxen and ibuprofen all had risk estimates in SSA between 1.5 and 2. Positive associations with case–control and spontaneous reports, but not SSA, were found for amphotericin B, omeprazole, metformin, amlodipine, ramipril, olmesartan, ciprofloxacin, valaciclovir, mycophenolate and diclofenac. All with the exception of metformin and omeprazole had risk estimates above 2.

Conclusion   This research highlights a number of medicines that may contribute to acute injury; however, we had an insufficient sample to confirm associations of some medicines. Spironolactone, furosemide, and trimethoprim with sulfamethoxazole are medicines that, in particular, need to be used carefully and monitored closely in patients in the community at risk of acute kidney injury.

Elizabeth E. Roughead
libby.roughead@unisa.edu.au

1 Clinical and Health Sciences, Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, SA, Australia
Key Points

One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a definitive list of nephrotoxic medicines, particularly one that provides a comparison of risks across medicines.

We identified 89 medicines suspected of causing acute kidney injury based on spontaneous report data with a reporting odds ratio above 2, from three different countries, with 21 associations confirmed by SSA or case–control studies using administrative health claims data.

Spironolactone, furosemide, and trimethoprim/sulfamethoxazole had the highest risk of acute kidney injury. They need to be monitored closely in patients in the community at risk of acute kidney injury.

1 Introduction

Acute kidney injury is a clinical syndrome associated with up to 15% of hospital admissions [1, 2], and occurs in up to 50% of persons in intensive care [3]. The development of acute kidney injury, even mild forms, is associated with poorer health outcomes in the longer term [4, 5], thus prevention of acute kidney injury is the first aim of care [4].

A number of factors have been associated with acute kidney injury, including patient characteristics, sepsis and shock, as well as medications [6]. Medications are thought to account for as much as 20% of all cases of community-acquired acute kidney injury [4]. Many of the factors associated with acute kidney injury are not modifiable, however medications represent one of the most easily modifiable risk factors; thus, being alert to the medicines that can contribute to acute kidney injury represents one opportunity for prevention [4].

Primary care provides an opportunity to prevent community-acquired acute kidney injury due to medicines. Studies suggest use of contraindicated medicines in persons with renal failure is frequent in primary care. A US study examined use of nephrotoxic medicines in persons with predialysis chronic kidney disease and found 72% were exposed to a potentially nephrotoxic medicine, with half prescribed two nephrotoxic medicines. [7] Furthermore, nephrotoxic medicine use in this population was associated with increased health service use and costs [7]. A systematic review involving 18 studies reported up to 37% of persons with renal impairment in primary care had inappropriate medicine use [8]. Inappropriate medicine use leads to significant harm.

Dutch study showed that 10% of medicine-related hospital admissions were due to renal impairment [9]. Renal failure has been found to be a significant predictor of readmissions due to adverse medicine reactions [10].

One of the barriers to proactive prevention of medicine-induced kidney injury in primary care is the lack of a definitive list of nephrotoxic medicines, particularly one that provides a comparison of risks across medicines. Lists have been generated based on literature review, expert opinion and pathological processes [11–18]. In the last few years, a number of authors have also reported lists of potentially nephrotoxic medicines based on associations generated from spontaneous reports of adverse medicine events [19–21]. These analyses provide opportunity to compare results across databases and create lists of nephrotoxic medicines with differential risk estimates because the studies used a consistent method and consistent data source. Spontaneous reports are effective in identifying new signals of adverse medication events but are limited by underreporting of events. Confirmation bias possibly restricts new medicines being identified, as to make a spontaneous report the reporter is required to first be suspicious that the event is an adverse event of the medicine and have sufficient motivation to report. Electronic health records offer a mechanism to confirm suspected associations between medicines and acute kidney injury, with electronic databases providing complete capture of both medicine use and the adverse event.

This study aimed to consolidate the evidence from the studies that used spontaneous report data to identify the range of medicines associated with acute kidney injury, with a particular focus on medicines used in primary care, and confirm the associations using administrative claims data.

Combinations of methods are recommended for confirming safety associations [22], with self-controlled methods considered to have higher predictive accuracy [23, 24]. Consistent with this, we used two different pharmacoepidemiological methods to determine the associations: sequence symmetry analysis (SSA), which mimics a within-person design and thus inherently adjusts for patient-specific founders, and a traditional pharmacoepidemiological design, the case–control study that has the advantage of overcoming small sample sizes.

2 Method

2.1 Spontaneous Report Studies

We searched the MEDLINE and EMBASE databases to identify all studies that had investigated all medicines associated with acute kidney injury from spontaneous adverse event reporting databases. Search terms included drug-related side effects or adverse reactions or drug-induced;
acute kidney injury or acute kidney failure; adverse drug reaction reporting systems or pharmacovigilance or drug surveillance programme or spontaneous report. The full search is included in electronic supplementary Tables 1 and 2.

We included studies that had identified the range of possible medicines that were associated with acute kidney injury, but excluded studies that had examined a single medicine class, single medicine or medicine interaction.

For each result, we extracted the medicine name or class, the disproportionality measure and 95% confidence interval (CI). The list of medicines associated with acute kidney injury was generated where at least one study had found a reporting odds ratio (ROR) above 2 and the CIs did not contain 1 [25].

2.2 Observational Studies

We used a self-controlled design, SSA, and a case–control design to confirm the associations identified from spontaneous reports.

Setting We used the Australian Government Department of Veterans’ Affairs administrative health claims database, which contains details of all prescription medicines, medical and allied health services, and hospitalisations provided to Department of Veterans’ Affairs clients for which the Department of Veterans’ Affairs pays a subsidy. The data cover a treatment population of approximately 250,000 clients.

The Study Period This study was conducted between 1 July 2005 and 30 June 2019.

The Primary Outcome Hospitalisations for acute kidney injury (primary diagnosis; International Classification of Diseases, Tenth Revision [ICD-10] code N17). We used the primary diagnosis code only, which indicates the cause of admission, and thus the primary outcome represents community-acquired acute kidney injury. Secondary diagnoses, which may include acute kidney injury that occurred during hospital stay, were not assessed because we did not have complete capture of medicines administered during hospital stay. The ICD-10 code N17 has been validated and shown to have high specificity but low-to-moderate sensitivity for acute kidney injury [26, 27].

The exposure Medicines identified as potentially nephrotoxic using data from the spontaneous reporting systems, i.e. medicines with an ROR above 2 and the CIs did not contain 1. Medicines used in the hospital setting only, such as parenteral antibiotics, were excluded from the analysis, as were medicines not available in Australia.

2.2.1 Study Design: Sequence Symmetry Analysis

The SSA is a self-controlled design that has been validated for adverse medicine event detection, showing moderate sensitivity, high specificity and robust performance [28, 29]. We examined the incident events of medicine exposure and hospitalisation for acute kidney injury, and included persons for whom both events occurred within a 12-month period.

SSA statistical methods For each medicine of interest, we calculated the sequence ratio [SR] by dividing the number of people who had acute kidney injury in the 12 months after initiation of the medicine by the number of people who had acute kidney injury in the 12 months before initiation of the medicine. To adjust for temporal changes in prescribing and hospitalisation trends over time, an adjusted SR [ASR] was calculated by dividing the crude SR by a null-effect SR [30]. The 95% CI was derived from bootstrapping with 10,000 samples of the ASR [31].

2.2.2 Study Design: Case–Control Study

We defined cases as persons who had their first hospitalisation for acute renal failure (ICD-10 code N17) in the study period, while controls were persons hospitalised for medical conditions other than acute renal failure in the same calendar year as the case. All cases and controls had at least one full year of claims history prior to the index admission.

Each case was matched to five controls by sex, age at date of admission (± 2 years) and year of admission (± 1 year). Cases could be controls prior to becoming a case, and controls were sampled with replacement. Medicine exposure was assessed in the year prior to the index date. We estimated medicine exposure based on the number of days supplied at the time of dispensings. The estimated days of supply was defined by the time period in which 75% of people returned for a repeat dispensing [19, 20]. For the majority of medicines in Australia, 1 month supply is provided under the national Pharmaceutical Benefits Scheme, and the time period within which 75% of people return is 35 days (the exposure period), allowing a 5-day grace period of non-adherence.

People were categorised into four groups: (1) new users were defined as people exposed at the time of admission (i.e. the supply period crossed the date of admission) and this was their first supply in that year; (2) current users were defined as persons who were on the medicine at the time of hospital admission but had previously had supplies during the year; (3) past users were defined as those who had had supplies previously in the year but did not have sufficient days supplied to cover the period, including the hospital admission; and (4) never users, i.e. persons with no dispensing of the medicine within the year prior to hospitalisation (see Fig. 1 in the electronic supplementary Appendix).
Case–Control Design Statistical Methods Descriptive statistics were used to report patient characteristics assessed at the time of hospital admission, including age, sex, residential status (living in the community or an aged care facility).

Conditional logistic regression was used to determine the association between exposure and acute kidney injury using non-exposure as the reference. The model was implemented once as a full model adjusting for other nephrotoxic medicines and number of dispensings of medicines in the year prior to the hospitalisation. ORs and 95% CIs were calculated for the medicines at a group and individual medicine level.

We used SAS version 9.4 (SAS Institute, Cary, NC, USA) to analyse the data.

3 Results

We located three studies that had all used RORs to identify potentially nephrotoxic medicines. The studies analysed data from the US FDA Adverse Event Reporting database [21], the Japanese Adverse Drug Event Report Database [19] and the French National Pharmacovigilance Database [20]. Across the three databases, there were 89 medicines that had an ROR above 2 in at least one database (Table 1).

Of the 89 medicines identified, 53 were able to be assessed in the Australian dataset.

For the SSA, populations were available over the entire study period. The number of people with both a medicine exposure and a hospital record for acute kidney injury ranged from 2 to 1798 (see electronic supplementary Table 3).

For the case–control study, a total of 7735 cases who were hospitalised with acute renal failure were matched by sex, age (± 2 years) and year of admission (± 1 year), with 38,675 controls (17,589 unique patients) without this condition at hospital admission. The median number of prescription dispensings in the year prior to admission was 84 for cases and 75 for controls. More cases than controls were living in a residential aged care facility prior to admission (22.5% vs. 16.9%). The full case–control results are available in electronic supplementary Table 4.

Spironolactone, furosemide, and trimethoprim with sulfamethoxazole were the three medicines with statistically significant associations using all methods. Spironolactone had the highest risk, with risk estimates of 3 or more by all methods, while furosemide and trimethoprim with sulfamethoxazole had risk estimates of 1.5 or more by all methods (Table 1).

We found positive associations for digoxin, perindopril, candesartan telmisartan, simvastatin, naproxen, ibuprofen, and zoledronic acid using SSA and spontaneous reports, but not for the case–control study. Zoledronic acid had the highest risk estimates, above 2, while candesartan telmisartan, simvastatin, naproxen and ibuprofen all had risk estimates in the SSA between 1.5 and 2 (Table 1).

We found positive associations for amphotericin B, omeprazole, metformin, amldopine, ramipril, olmesartan, ciprolfloxacin, valaciclovir, mycophenolate and diclofenac using the case–control design and spontaneous reports, but not for the SSA. With the exception of metformin and omeprazole, all had risk estimates in the case–control study above 2.

Results for medicines that were positive in the spontaneous reports but not assessable in our dataset are included in electronic supplementary Table 6.

4 Discussion

Our study focused on medicines that put people at risk of admission to hospital for acute kidney injury and the comparative risks across medicines. Three medicines, spironolactone, furosemide, spironolactone and sulfamethoxazole with trimethoprim, were associated with acute kidney injury across all three methods, with spironolactone having the highest risk.

Risk estimates above 2 by at least two methods were also found for zoledronic acid, amphotericin B, amldopine, ramipril, olmesartan, ciprolfloxacin, valaciclovir, mycophenolate and diclofenac. Other epidemiological studies confirm these associations. A New Zealand study showed a fourfold elevated risk of acute kidney injury where an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker was started in the previous 7 days (adjusted OR 4.07, 95% CI 3.37–4.93), and a sixfold increase in risk for initiation of a diuretic in the previous 7 days (adjusted OR 6.31, 95% CI 5.46–7.29) [32]. This same study found a sevenfold elevated risk for starting non-steroidal anti-inflammatory drugs (NSAIDs) in the previous 7 days (adjusted OR 7.30, 95% CI 6.59–8.10).

One of the challenges in assessing the nephrotoxic nature of medicines is that the medicines implicated, such as medicines affecting the renin angiotensin system, are frequently used to treat morbidities that make people more at risk of acute kidney injury, such as diabetes and heart failure; thus, confounding by indication can be a factor affecting associations. Patient-related precipitating factors, such as infection, dehydration or exacerbation of an illness such as heart failure, may also have confounded the results observed [33, 34]. However, we included SSA as a method to control for patient-specific confounding, which suggests the addition of the medicine was a contributor independent of the disease. These associations are further confirmed by our case–control study, which showed the risk was highest in new users (electronic supplementary Results), as well as the observations from spontaneous reporting systems in three countries.
Table 1  Medicines and their association with acute kidney injury

| ATC code—main systemic | Medication | US FDA adverse drug event reporting system | Japanese adverse drug event reporting system | French adverse drug event reporting system | No. of databases in which the ROR was ≥2 and lower 95% CI >1 | SSA result, Australian ASR (95% CI) | Case–control result (new users vs. non-users) [OR (95% CI)] |
|------------------------|------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|
|                        |            |                                                             |                                             |                                             |                                                              |                                      |                                                                            |
| Positive results in spontaneous reports, sequence symmetry and case–control methods |
| C03DA01                | Spironolactone | 8.97 [8.24–9.77] | 7.36 [6.12–8.86] | 10.54 [7.39–15.03] | 3 | 2.96 (2.59–3.40) | 3.45 (3.01–3.95) |
| C03CA01                | Furosemide | 12.61 [11.94–13.32] | 4.23 [3.60–4.96] | 16.5 [13.63–19.99] | 3 | 1.86 (1.68–2.06) | 3.97 (3.54–4.45) |
| J01EE01                | Sulfamethoxazole and trimethoprim | 6.96 [6.38–7.59] | 4.17 [3.25–5.36] | 2 | 1.56 (1.29–1.89) | 17.37 (9.67–31.2) |
| Positive results by the sequence symmetry and spontaneous reports methods |
| C09CA06                | Candesartan | 4.49 [3.56–5.66] | 10.88 [7.28–16.25] | 2 | 1.76 (1.30–2.37) | Not assessable |
| M01AE02                | Naproxen | 0.63 (0.59–0.68) | 3.68 [1.96–6.9] | 1 | 1.67 (1.05–2.68) | 1.99 (0.95–4.19) |
| M01AE01                | Ibuprofen | 3.15 (3.01–3.30) | 2.03 [1.35–3.05] | 2 | 1.56 (1.07–2.27) | 1.49 (0.69–3.22) |
| M05BA08                | Zoledronic acid | 2.23 (2.15–2.31) | 2.92 [1.52–5.6] | 2 | 2.52 (1.63–3.89) | 0.99 (0.8–1.23) |
| C01AA05                | Digoxin | 5.77 (5.45–6.10) | 1 | 1.41 (1.19–1.66) | Not assessable |
| C09AA04                | Perindopril | 6.95 [5.35–9.03] | 1 | 1.41 (1.20–1.66) | Not assessable |
| C09CA07                | Telmisartan | 3.85 [1.51–9.78] | 1 | 1.60 (1.16–2.21) | Not assessable |
| C10AA01                | Simvastatin | 4.06 (3.88–4.25) | 1 | 1.53 (1.04–2.23) | 1.69 (0.75–3.85) |
| Positive results by the case-control and spontaneous reports methods |
| A01AB04                | Amphotericin B | 8.08 (7.33–8.91) | 1 | No pairs | 4.41 (1.91–10.21) |
| A02BC01                | Omeprazole | 2.35 (2.19–2.53) | 1 | 0.93 (0.77–1.12) | 1.57 (1.04–2.37) |
| A10BA02                | Metformin | 10.65 (10.31–11.00) | 5.17 [3.89–6.86] | 2 | 1.02 (0.71–1.46) | 1.72 (1.04–2.83) |
| C09CA01                | Amlodipine | 2.32 (2.18–2.48) | 3.26 [2.29–4.64] | 2 | 0.64 (0.55–0.75) | 2.39 (1.66–3.43) |
| C09AA02                | Enalapril | 8.32 (7.57–9.16) | 4.21 [2.29–7.72] | 2 | 1.26 (0.65–2.47) | 2.02 (0.5–8.18) |
| C09AA05                | Ramipril | 7.10 (6.69–7.53) | 5.81 [4.26–7.92] | 2 | 1.03 (0.85–1.25) | 2.02 (1.27–3.21) |
| C09CA08                | Olmesartan | 5.08 (4.65–5.56) | 7.55 [5.5–10.37] | 2 | 1.59 (0.89–2.82) | 4.51 (1.56–13.04) |
| C09CA03                | Valsartan | 3.05 (2.88–3.23) | 2.15 [1.72–2.69] | 6.36 [4.28–9.47] | 3 | 2.77 (0.74–10.4) | 1.03 (0.09–11.55) |
| J01MA02, J05BA11       | Ciprofloxacin | 2.4 (2.30–2.63) | 1.94 [1.2–3.14] | 1 | 1.08 (0.41–2.79) | 3.99 (2.48–6.42) |
| L04AA06                | Mycophenolic acid | 9.53 (8.76–10.38) | 4.36 [2.48–7.65] | 3 | 1.07 (0.73–1.56) | 2.48 (1.34–4.57) |
| M01AB05                | Diclofenac | 4.05 (3.82–4.30) | 4.38 [3.78–5.08] | 6.27 [4.29–9.16] | 3 | 0.88 (0.27–2.89) | 3.05 (1.75–5.32) |
| Positive results by the spontaneous reports methods |
| J05BA01                | Acioclor | 8.60 (7.93–9.32) | 11.17 [9.55–13.10] | 23.25 [15.12–35.77] | 3 | 1.72 (0.92–3.23) | 4.91 (0.81–29.71) |
| C09AA03                | Lisinopril | 4.24 (3.99–4.50) | 7.02 [3.08–16.01] | 2 | 2.00 (0.85–4.73) | 1.07 (0.1–12.04) |
| L04AD02                | Tacrolimus | 4.40 (4.21–4.60) | 2.59 [1.39–4.8] | 2 | 1.91 (0.46–7.99) | Not assessable |
| L04AX03, L01BA01       | Methotrexate | 2.59 (2.41–2.78) | 2.15 [1.54–2.98] | 2 | 1.85 (0.85–4.05) | 0.99 (0.54–1.82) |
| ATC code—main systemic | Medication          | US FDA adverse drug event reporting system | Japanese adverse drug event reporting system | French adverse drug event reporting system | No. of databases in which the ROR was ≥2 and lower 95% CI >1 | SSA result, Australian ASR (95% CI) | Case–control result (new users vs. non-users) [OR (95% CI)] |
|------------------------|---------------------|-------------------------------------------|---------------------------------------------|-------------------------------------------|------------------------------------------------------------|----------------------------------|-----------------------------------------------------|
| N05AN01                | Lithium            | 8.86 (8.15–9.64)                           | 2.14 [1.3–3.5]                              | 2                                         | No pairs                                                  | 0.88 (0.24–3.21)                  |                                                    |
| A02BA03                | Famotidine         | 2.47 [1.99–3.07]                           |                                             | 1                                         | 0.65 (0.33–1.26)<sup>a</sup>                              | Not assessable                   |                                                    |
| A10BB09                | Gliclazide         | 3.16 [1.52–6.57]                           |                                             | 1                                         | 0.52 (0.38–0.71)                                           | Not assessable                   |                                                    |
| A10BH01                | Sitagliptin        | 2.23 [1.13–4.41]                           |                                             | 1                                         | 1.47 (0.81–2.68)<sup>a</sup>                              | Not assessable                   |                                                    |
| B01AE07                | Dabigatran         | 2.18 (2.09–2.27)                           |                                             | 1                                         | 1.24 (0.53–2.92)<sup>a</sup>                              | Not assessable                   |                                                    |
| C03AA03                | Hydrochlorothiazide | 6.39 [5.05–8.09]                          |                                             | 1                                         | 1.19 (0.94–1.51)                                           | Not assessable                   |                                                    |
| C03BA11                | Indapamide         | 2.36 [1.28–4.38]                           |                                             | 1                                         | 1.30 (0.89–1.90)                                           | Not assessable                   |                                                    |
| C03DA04                | Eplerenone         | 27.42 [11.62–64.68]                        |                                             | 1                                         | 0.55 (0.14–2.19)<sup>a</sup>                              | Not assessable                   |                                                    |
| C09CA01                | Losartan           | 7.35 [3.67–14.71]                          |                                             | 1                                         | 1.0 (0.06–15.9)                                            | Not assessable                   |                                                    |
| C09CA04                | Irbesartan         | 3.99 [2.55–6.25]                           |                                             | 1                                         | 1.10 (0.87–1.38)                                           | Not assessable                   |                                                    |
| C10AB05                | Fenofibrate        | 2.5 [1.09–5.76]                            |                                             | 1                                         | 1.98 (0.93–4.23)<sup>a</sup>                              | Not assessable                   |                                                    |
| J01DD04                | Ceftriaxone        | 4.66 (4.30–5.06)                           |                                             | 1                                         | 0.65 (0.57–0.74)                                           | Not assessable                   |                                                    |
| J04AB02                | Rifampicin, rifampin | 2.42 [1.62–3.63]                           |                                             | 1                                         | 1.18 (0.65–2.16)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01AA03                | Melphalan          | 4.08 [1.94–8.55]                           |                                             | 1                                         | 1.07 (0.39–2.95)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01BA04                | Pemetrexed         | 4.31 [2.4–7.73]                            |                                             | 1                                         | 2.66 (0.52–13.7)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01BC05                | Gemcitabine        | 2.99 [1.69–5.3]                            |                                             | 1                                         | 1.44 (0.61–3.42)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01CB01                | Etoposide          | 2.06 [1.15–3.71]                           |                                             | 1                                         | 1.34 (0.46–3.85)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01XA01                | Cisplatin          | 1.73 [1.52–1.98]                           | 10.46 [7.4–14.79]                          | 1                                         | 2.62 (0.93–7.34)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01XA02                | Carboplatin        | 2.19 (2.02–2.38)                           |                                             | 1                                         | 1.94 (0.96–3.93)<sup>a</sup>                              | Not assessable                   |                                                    |
| L01XX32                | Bortezomib         | 2.48 (2.34–2.62)                           |                                             | 1                                         | 0.38 (0.15–0.95)<sup>a</sup>                              | Not assessable                   |                                                    |
| M04AC01                | Colchicine         | 7.33 [5.1–10.54]                           |                                             | 1                                         | 1.17 (0.96–1.42)                                           | Not assessable                   |                                                    |
| M05BA03                | Pamidronate acid   | 5.38 (5.06–5.72)                           |                                             | 1                                         | 0.41 (0.17–1.01)<sup>a</sup>                              | 1.34 (0.2–8.98)                  |                                                    |
| V03AC03                | Deferasirox        | 4.29 (4.11–4.48)                           |                                             | 1                                         | 1.92 (0.17–21.2)<sup>a</sup>                              | Not assessable                   |                                                    |

<sup>a</sup>Fewer than 50 pairs

**ATC** Anatomical Therapeutic Chemical, **SSA** sequence symmetry analysis, **ASR** adjusted sequence ratio, **OR** odds ratio, **CI** confidence interval, **ROR** reporting odds ratio
The dosage of the medicine used may also have been a factor contributing to the risk of acute kidney disease. An Australian study among persons with renal impairment who were admitted to hospital found that for persons aged 40 years and over with either hypertension or poor renal function (a creatinine clearance of ≤60 mL/min), 32% were receiving a medicine that required renal adjustment or was potentially nephrotoxic at the time of admission; 16% were receiving a contraindicated medicine and 21% were inappropriately dosed [35]. A UK study found similar estimates among persons with a creatinine clearance of ≤60 mL/min in general practice, with 25% requiring a dosage change, discontinuation of the medicine, or change to a safer alternative [36]. Even higher estimates of inappropriate dosage among persons with renal impairment have been identified when specific medicines are studied [37]. We did not have a dataset sufficiently large enough to enable stratification by dose, thus further research identifying the effect of dose on the associations is required.

We synthesized findings from three studies that had assessed nephrotoxic medicines from spontaneous reports. While we could assess the majority of medicines that were identified in all three studies or at least two of the studies, there were a number of medicines that were only identified in one of the spontaneous report studies and could not be confirmed by our methods because of lack of availability of the medicines in Australia or lack of events due to small sample sizes. These potential associations need to be confirmed in larger datasets. The US study of spontaneous reports classified their findings into known, possible and possible new nephrotoxins [21]. Known nephrotoxins were those reported in three of four medicine information sources reviewed, while possible nephrotoxins were identified in two sources. Of those identified as possible new nephrotoxins, our sequence symmetry results were positive for two medicines, i.e., digoxin and zoledronic acid, but the case–control results did not confirm the association for zoledronic acid and could not be assessed for digoxin. Both zoledronic acid and digoxin are medicines that require dosage adjustment in persons with renal impairment and it may be that lack of dosage adjustment was a contributing causal factor, highlighting the need for continuous monitoring of renal function and dosage adjustment where necessary in persons on long-term therapy.

A strength of our study results is that the data represent findings from different datasets and across four different countries, increasing the likelihood that our results are generalisable to the larger population. However, a limitation of our study was the sample available. While our database included 250,000 persons and 15 years of history (3.75 million person-years), for many medicines the events were too infrequent for us to obtain reliable estimates. Large or multinational analyses are required to confirm associations between medicines within classes. Our study relied on identification of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in missed cases of acute kidney injury as recorded by trained coders using the ICD codes. This may have resulted in
Declarations

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This research was funded by the Australian Government Department of Veterans’ Affairs as part of the Veterans Medicines Advice and Therapeutics Education Services (MATES) Program. The Australian Government Department of Veterans’ Affairs reviewed the manuscript prior to submission.

Conflicts of interest/competing interests Elizabeth E. Roughead, Mhairi Kerr, Anna Moffat, Gizat M. Kassie and Nicole Pratt have no conflicts of interest to declare.

Ethics approval This research was approved by the University of South Australia Human Research Ethics Committee (P203-04) and the Departments of Defence and Veterans’ Affairs Human Research Ethics Committee (E016-007).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The Australian Government Department of Veterans’ Affairs are the owners of the data. Requests for data would need to be made directly to the Australian Government Department of Veterans’ Affairs

Code availability The code created for this analysis is available on request to the authors.

Author contributions ER conceived and designed the research, interpreted the results, and drafted and finalised the manuscript. NP designed the research, interpreted the results, and critically reviewed the manuscript. MK contributed to the study design, created all study code, undertook all analyses, and assisted with data interpretation and manuscript review. AM contributed to data interpretation and synthesis, as well as manuscript development and review. GK contributed to data interpretation and synthesis, as well as manuscript development and review. All authors read and approved the final version.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

References

1. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014;9(6):1007–14. https://doi.org/10.2215/CJN.07920713.
2. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol. 2014;9(1):12–20. https://doi.org/10.2215/CJN.07230313.
3. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23. https://doi.org/10.1007/s00134-015-3934-7.
4. 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. Nat Rev Nephrol. 2017;13(4):241–57. https://doi.org/10.1038/nrneph.2017.2.
5. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med. 2014;189(9):1075–81. https://doi.org/10.1093/ajrccm/ccu052.
6. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol. 2018;14(10):607–25. https://doi.org/10.1038/s41581-018-0052-0.
7. Davis-Ajami ML, Fink JC, Wu J. Nephrotoxic medication exposure in U.S. adults with predialysis chronic kidney disease: health services utilization and cost outcomes. J Manag Care Spec Pharm. 2016;22(8):959–68. https://doi.org/10.18553/jmc.2016.22.8.959.
8. Dorks M, Allers K, Schmiedmayer G, Herget-Rosenthal S, Hoffmann F. Inappropriate medication in non-hospitalized patients with renal insufficiency: a systematic review. J Am Geriatr Soc. 2017;65(4):853–62. https://doi.org/10.1111/jgs.14809.
9. Leendertse AJ, van Dijk EA, De Smet PA, Egberts TC, van den Berst PM. Contribution of renal impairment to potentially preventable medication-related hospital admissions. Ann Pharmacother. 2012;46(5):625–33. https://doi.org/10.1345/aph.1Q633.
10. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Curtain CM, Bereznicki LR. Repeat adverse drug reaction-related hospital admissions in elderly Australians: a retrospective study at the royal Hobart hospital. Drugs Aging. 2017;34(10):777–83. https://doi.org/10.1007/s40266-017-0490-6.
11. Gray MP, Barreto EF, Schreier DJ, Kellum JA, Suh K, Kashani KB, et al. Consensus obtained for the nephrotoxic potential of 167 drugs in adult critically ill patients using a modified Delphi method. Drug Saf. 2022;45(4):389–98. https://doi.org/10.1007/s40264-022-01174-4.
12. Perazella MA, Rosner MH. Drug-induced acute kidney injury. Clin J Am Soc Nephrol. 2022;17(8):1220–33. https://doi.org/10.2215/CJN.11290821.
13. Schetz M, Dasta J, Goldstein S, Golper T. Drug-induced acute kidney injury. Curr Opin Crit Care. 2005;11(6):555–65. https://doi.org/10.1097/01.ccx.0000184300.68383.95.
14. Singh NP, Ganguli A, Prakash A. Drug-induced kidney diseases. J Assoc Physicians India. 2003;51:970–9.
15. Khan S, Loi V, Rosner MH. Drug-induced kidney injury in the elderly. Drugs Aging. 2017;34(10):729–41. https://doi.org/10.1007/s40266-017-0484-4.
16. Paukeksakon P, Fogo AB. Drug-induced nephropathies. Histopathology. 2017;70(1):94–108. https://doi.org/10.1111/his.13064.
17. Sales GTM, Forresto RD. Drug-induced nephotoxicity. Rev Assoc Med Bras (1992). 2015. 12.
18. Hoofstra S, Reza M, Liao W, Schmitz F, Deters K. Surveillance of drugs that most frequently induce acute kidney injury: a pharmacovigilance approach. J Clin Pharm Ther. 2019;44(1):49–53. https://doi.org/10.1111/jcpt.12748.
20. Pierson-Marchandise M, Gras V, Moragony J, Micallef J, Gaboriau L, Picard S, et al. The drugs that mostly frequently induce acute kidney injury: a case–noncase study of a pharmacovigilance database. Br J Clin Pharmacol. 2017;83(6):1341–9. https://doi.org/10.1111/bcp.13216.

21. 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. https://doi.org/10.1002/phar.2152.

22. Schuemie MJ, Coloma PM, Straatman H, Herings RM, Trifiro G, Matthews JN, et al. Using electronic health care records for drug safety signal detection: a comparative evaluation of statistical methods. Med Care. 2012;50(10):890–7. https://doi.org/10.1097/MLR.0b013e31825f63bf.

23. Arnaud M, Begaud B, Thurin N, Moore N, Pariente A, Salvo F. Methods for safety signal detection in healthcare databases: a literature review. Expert Opin Drug Saf. 2017;16(6):721–32. https://doi.org/10.1080/14740338.2017.1325463.

24. Ryan PB, Stang PE, Overhage JM, Suchard MA, Hartzema AG, DuMouchel W, et al. A comparison of the empirical performance of methods for a risk identification system. Drug Saf. 2013;36(Suppl 1):S143–58. https://doi.org/10.1007/s40264-013-0108-9.

25. Böhm R. Primer on disproportionality analysis version: 2018–10-16. Kiel: Kiel University; 2018.

26. Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, et al. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. BMJ Open. 2012. https://doi.org/10.1136/bmjopen-2012-001821.

27. Ko S, Venkatesan S, Nand K, Levidiotis V, Nelson C, Janus E. International statistical classification of diseases and related health problems coding underestimates the incidence and prevalence of acute kidney injury and chronic kidney disease in general medical patients. Intern Med J. 2018;48(3):310–5. https://doi.org/10.1111/imj.13729.

28. Wahab IA, Pratt NL, Wiese MD, Kalisch LM, Roughhead EE. The validity of sequence symmetry analysis (SSA) for adverse drug reaction signal detection. Pharmacoepidemiol Drug Saf. 2013;22(5):496–502. https://doi.org/10.1002/pds.3417.

29. Lai ECC, Pratt N, Hsieh CY, Lin SJ, Pottegard A, Roughhead EE, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. Eur J Epidemiol. 2017;32(7):567–82. https://doi.org/10.1007/s10654-017-0281-8.

30. Tsiroupolous I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. Pharmacoepidemiol Drug Saf. 2009;18(6):483–91. https://doi.org/10.1002/pds.1736.

31. Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM. Nocturnal leg cramps and prescription use that precedes them: a sequence symmetry analysis. Arch Intern Med. 2012;172(2):120–6. https://doi.org/10.1001/archinternmed.2011.1029.

32. Tomlin AM, Reith DM, Woods DJ, Lloyd HS, Smith A, Fountain JS, et al. A pharmacoepidemiology database system for monitoring risk due to the use of medicines by New Zealand primary care patients. Drug Saf. 2017;40(12):1259–77. https://doi.org/10.1007/s40264-017-0579-1.

33. Robert L, Ficheur G, Gautier S, Servais A, Luyckx M, Soula J, et al. Community-acquired acute kidney injury induced by drugs in older patients: a multifactorial event. Clin Interv Aging. 2019;14:2105–13. https://doi.org/10.2147/CIA.S217567.

34. Cely JE, Mendoza EJ, Sprockel JJ, Perez LC, Mateus JM, Maldonado S, et al. Risk factors for community-acquired acute kidney injury in medical patients: a nested case-control study. Blood Purif. 2020;49(6):677–84. https://doi.org/10.1159/000506502.

35. Doody HK, Peterson GM, Watson D, Castelino RL. Retrospective evaluation of potentially inappropriate prescribing in hospitalized patients with renal impairment. Curr Med Res Opin. 2015;31(3):525–35. https://doi.org/10.1185/03007995.2015.1010836.

36. Wood S, Petty D, Glidewell L, Raynor T. Are we over-dosing our elderly patients with renally excreted drugs in primary care? Int J Pharmacy Pract. 2011;19(Suppl 2):38. https://doi.org/10.1111/j.2042-7174.2011.00147_1.x.

37. Wood S, Petty D, Glidewell L, Raynor DT. Application of prescribing recommendations in older people with reduced kidney function: a cross-sectional study in general practice. Br J Gen Pract. 2018;68(670):e378–87. https://doi.org/10.3399/bjgp18X695993.

38. UK Renal Registry. Guidelines for medicines optimisation in patients with acute kidney injury. London: UK Renal Registry; 2016.