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Original Article

ORIGINAL ARTICLE

Associations between acute kidney injury and bone fractures: a retrospective cohort study

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ABSTRACT

Background. Acute kidney injury (AKI) is common. An AKI episode may disrupt the normal mineral bone balance maintained by normal kidney function, thereby modifying the risk of developing bone fractures. However, it remains unclear whether an AKI episode is associated with the risk of bone fractures.

Methods. Using retrospective cohort study from an Australian Local Health District, we examined the association between an AKI episode and bone fractures using patient data between 2008 and 2017. Time-varying Cox proportional hazards and propensity-matched analysis were used to examine the association. Sensitivity analyses were undertaken to capture the impact of confirmed AKI status and AKI severity.

Results. Of 123 426 included patients, 14 549 (12%) had an AKI episode and 12 505 (10%) had a bone fracture. In the unadjusted analysis, AKI was associated with bone fractures [hazard ratio (HR) 1.99, 95% confidence interval (CI) 1.88–2.11]. This association persisted in the adjusted analysis (HR 1.50, 95% CI 1.41–1.59) and propensity-matched dataset (HR 1.71, 95% CI 1.59–1.83). The sensitivity analysis yielded similar results, with the AKI patients having a higher risk of fractures compared with no AKI patients in the adjusted analysis (HR 1.34, 95% CI 1.25–1.43) and in the propensity-matched dataset (HR 1.44, 95% CI 1.33–1.55). Similar results were seen in the subsidiary sensitivity analysis excluding patients without baseline creatinine. We did not find an increased risk of bone fractures with increasing AKI severity ($P = .7$). Interaction tests demonstrated a significant association between sex and age category with AKI status and fractures, but not CKD stage or osteoporosis.

Conclusions. AKI is associated with a greater risk of bone fractures. This could have implications for managing and screening for bone disease in patients post-AKI episode. This association should be examined in other cohorts and populations for verification.

Keywords: acute kidney injury, AKI severity, bone mineral balance, bone mineral disorders, fractures

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KEY LEARNING POINTS

What was known:

- An acute kidney injury (AKI) episode is associated with several adverse health outcomes, including progression of kidney disease, increased risk of cardiovascular events and death.
- Chronic kidney disease (CKD) and AKI share similar and interconnected adverse event profiles.
- However, while mineral bone disorders have been clearly established in chronic CKD, it remains poorly studied in AKI.

This study adds:

- Using a retrospective population cohort, covering a 10-year period, we examined the risk of bone fractures following an episode of AKI.
- We found a significant risk of bone fractures following an episode of AKI.
- The association remained valid in multivariable analysis, propensity-matched cohort and during sensitivity and subsidiary analysis.

Potential impact:

- Bone fractures and possible bone mineral disorders should be added to adverse event profile after an episode of AKI.
- This could have implications in managing and screening for bone disease in patients post-AKI episode.

INTRODUCTION

The kidney is the principal organ responsible for maintaining homeostasis, with chronic disruptions of kidney function called chronic kidney disease (CKD). CKD is defined by an estimated glomerular filtration rate (eGFR) $\leq$60 mL/min per 1.73 m^2 and/or a urine albumin-to-creatinine ratio of $\geq$30 mg/mmol [1]. The presence of CKD is a significant risk factor for cardiovascular disease, progression to kidney failure (KF) and mortality [2–5]. CKD is also a risk factor for developing mineral bone disorder (MBD), also known as CKD-MBD [6]. CKD-MBD is reflected clinically as an increased risk of bone fractures, with an increasing risk as the severity of CKD advances [7, 8].

Acute disruptions of kidney function is defined as acute kidney injury (AKI) and graded as stage 1, 2 or 3 based on changes in creatinine from baseline and urine output [9]. AKI complicates around 20% of hospital admissions [10], with an increasing prevalence over time [11, 12]. Similar to CKD, several adverse health outcomes have been associated with AKI exposure, including the development and progression of kidney disease, increased risk of death and cardiovascular events [13–15].

There is strong evidence that AKI and CKD have a similar and interconnected adverse event profile. Both AKI and CKD have an increased risk of cardiovascular disease, mortality and kidney disease progression, with similar mechanisms linking the disease process with the adverse event. However, MBD remains one association clearly examined and established in CKD which is poorly studied in AKI. Only one study to date examined the risk of bone fractures (a surrogate marker for MBD) following an AKI episode [16]. While a significant association was shown, the study only focused on patients surviving an AKI requiring dialysis episode and compared them with no AKI patients, therefore missing the vast majority of patients who present with less severe AKI.

An examination of AKI and fracture risk is important. The association between AKI and CKD, and adverse events and pathophysiology mechanisms is incomplete without an examination of the association of AKI with MBD. This approach also emphasizes the need to view AKI not merely as a transient reversible disorder, but as a consequential condition that may precipitate long-term health issues, necessitating ongoing monitoring and evaluation, including bone health.

We therefore set out to examine the association between AKI exposure on the risk of fractures in a retrospective cohort derived from a local health population in Australia. We hypothesized that an episode of AKI is an independent risk factor for future bone fractures.

MATERIALS AND METHODS

Study cohort

A retrospective population-based cohort study was carried out using longitudinal data from an Australian regional health service, the Illawarra Shoalhaven Local Health District (ISLHD). We included patients ($\geq$18 years of age) who presented to the ISLHD hospitals or emergency departments or who had a laboratory test using the health district laboratory services between 1 January 2008 through 31 December 2017. This study was approved by the ISLHD/University of Wollongong Human research ethics committee (HREC 2018/409) and conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

We defined the index date as 180 days after date of first presentation to create a 180-day washout period free of AKI and fractures. This approach ensured baseline creatinine levels were available to determine AKI and CKD status. Additionally, it allowed a minimum of 6 months of follow-up and avoided the risk of a bone fracture outcome occurring prior to an AKI exposure.

We excluded patients: (i) non-residents of the ISLHD, (ii) on renal replacement therapy at the start of the study, (iii) with missing information relating to laboratory and International Classification of Diseases–Tenth Revision (ICD-10) coding, (iv) who had an AKI diagnosis 30 days pre- or post-fracture diagnosis (since the AKI episode may be related to the fracture episode), (v) aged more than 100 years, (vi) with documented AKI or fracture prior to 2008 and (vii) with follow-up ending before the 180-day washout period.

Data sources and baseline variables

Routinely collected de-identified existing data were extracted from the Illawarra Health Information Platform (IHIP). IHIP is a non-identifiable databank established by the ISLHD and the University of Wollongong for research, planning and evaluation

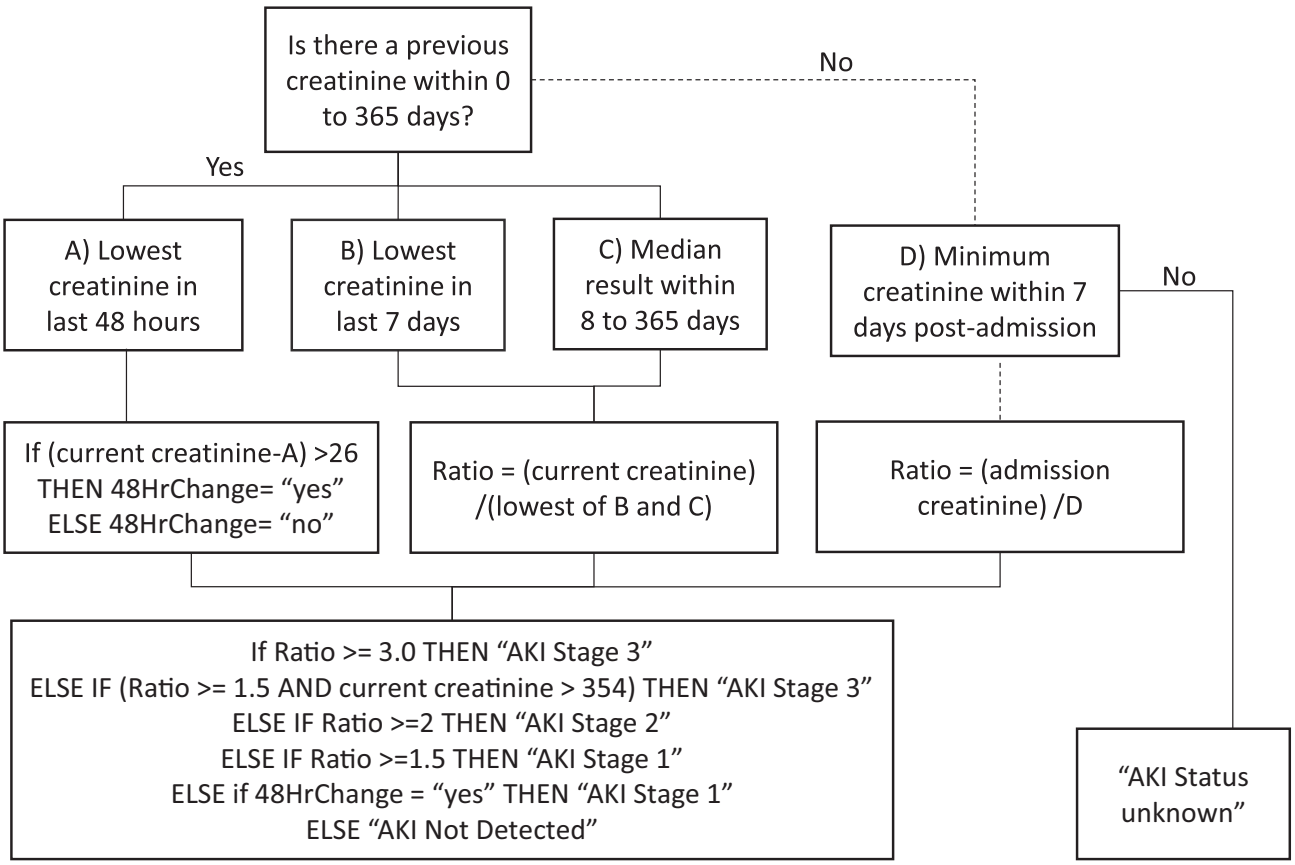

Figure 1: Flowchart for derivation of AKI cohort based on creatinine (μmol/L) pathology. Dashed line represents modification to original flowchart to identify patients with a first time AKI hospital admission.

purposes. Data from health district laboratory services and IHIP were linked for a final de-identified dataset. Laboratory test data from 2007 to 2017 was used, 1 year prior to study cohort start date, to capture baseline creatinine for estimation of AKI and CKD prior to fracture presentation.

Creatinine measurements were used to determine an AKI episode and ICD-10, Australian Modification (ICD-10-AM) codes from hospitalized admissions were used to create a baseline e-phenotype picture using comorbidities for each patient (Supplementary data, Table S1). Baseline variables were sex, age (at first laboratory test or hospital presentation), urbanity (major city or regional) and socio-economic indexes for areas [SEIFA, measured by Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) and categorized into tertiles of high, middle and low, with higher scores reflecting higher socioeconomic status]. Urbanity and IRSAD were determined from the postcode of patients' residential addresses, using the Accessibility/Remoteness Index of Australia taken from the Australian Bureau of Statistics using Australian Standard Geographical Classification from census data [18]. Comorbidities were identified from the 180-day washout period and included as baseline demographics.

Definitions

Our exposure was an episode of AKI, diagnosed using ICD-10-AM codes or based on creatinine measurements, with the first AKI episode used. We adapted the National Health Service–endorsed laboratory based AKI algorithm (Fig. 1) (developed to prospectively identify an episode of AKI) [19]. We adapted the flowchart for use in Australia [20] after modification to capture patients who presented to hospital with an AKI episode and with no previous creatinine measurement [21]. Patients who did not have an AKI based on laboratory tests or ICD-10-AM coding were classified as not having an AKI. CKD was defined as per ICD-10 coding or KDIGO definition based on serum creatinine [1] and sub grouped as per eGFR into <30, 30–60 and >60.

The primary outcome was fracture. Fracture was diagnosed using ICD-10-AM coding (Supplementary data, Table S1) with the first fracture episode used for each patient. We excluded fractures associated with trauma such as skull, facial and digital fractures, as well as pathological fractures due to malignancy (Supplementary data, Table S1). Patients were censored at the death, commencement of renal replacement therapy or last follow-up visit.

Statistical analysis

Categorical data were expressed as numbers (percentages) and compared using chi-square test. Continuous data were expressed as mean with standard deviation or median with interquartile range and analysed as per distribution using Student's *t*-test and the Mann–Whitney U test. Bone fracture rates were expressed as events [95% confidence interval (CI)] per 1000

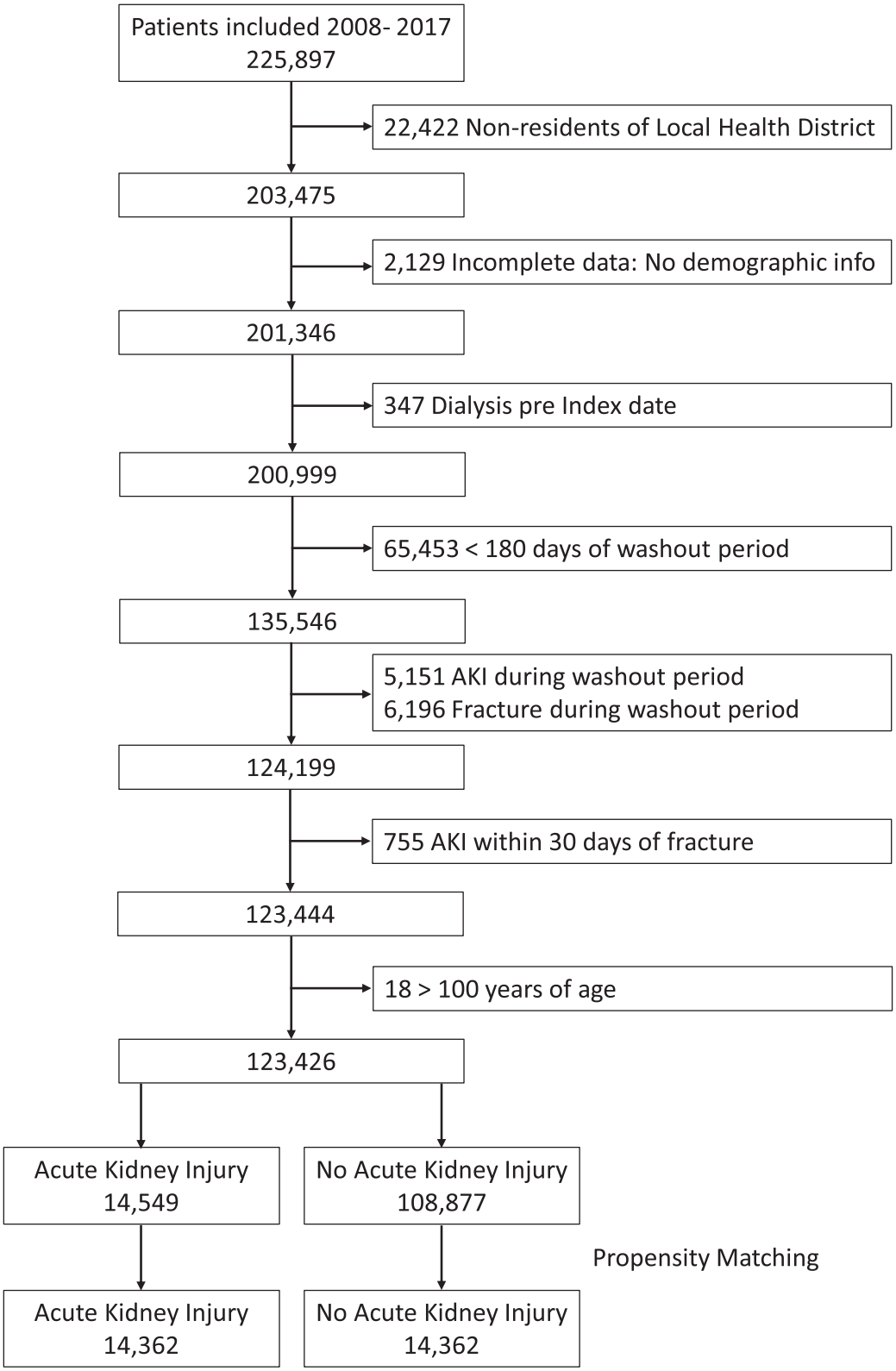

Figure 2: Cohort selection flow diagram. Serial exclusion criteria to derive the final study cohort.

Table 1: Baseline characteristics of patients with and without AKI for full cohort and after propensity matching.

	Full cohort			After propensity matching		
	No AKI ($n = 108\,877$)	AKI ($n = 14\,549$)	SD	No AKI ($n = 14\,362$)	AKI ($n = 14\,362$)	SD
Sex (male)	45 479 (42%)	7805 (54%)	0.24	7601 (53%)	7677 (54%)	0.01
Age (years)	50.9 (20.8)	68.8 (15.8)	0.97	69.9 (15.6)	68.6 (15.6)	0.07
<30	22 881 (21%)	498 (3%)	0.94	446 (3%)	498 (4%)	0.05
30–<50	29 311 (27%)	1215 (8%)		1124 (8%)	1215 (9%)	
50–70	32 894 (30%)	4821 (33%)		4456 (31%)	4813 (34%)	
>70	23 791 (22%)	8015 (55%)		8336 (58%)	7836 (55%)	
Urbanity			0.03			0.02
Major city	70 868 (65%)	9696 (67%)		9401 (66%)	9551 (67%)	
Regional	38 009 (35%)	4853 (33%)		4961 (35%)	4811 (33%)	
IRSAD			0.005			0.01
Low	32 312 (30%)	4291 (30%)		4358 (30%)	4242 (30%)	
Middle	34 464 (32%)	4720 (32%)		4554 (32%)	4662 (33%)	
High	42 101 (39%)	5538 (38%)		5450 (38%)	5458 (38%)	
Comorbidities						
CKD	3845 (4%)	3249 (22%)	0.58	2722 (19%)	3064 (21%)	0.07
>60	105 032 (97%)	11 300 (78%)	0.57	11 640 (81%)	11 298 (79%)	0.09
30–60	3483 (3%)	2542 (18%)		2387 (17%)	2485 (17%)	
<30	362 (0.3%)	707 (5%)		335 (2%)	581 (4%)	
Hypertension	8350 (8%)	2637 (18%)	0.32	2319 (16%)	2516 (18%)	0.04
Diabetes	4892 (5%)	1806 (12%)	0.29	1512 (11%)	1701 (12%)	0.05
CAD	3923 (4%)	1092 (8%)	0.17	940 (7%)	1039 (7%)	0.03
CHD	1147 (1%)	809 (6%)	0.25	575 (4%)	710 (5%)	0.05
Arrythmia	3917 (4%)	1351 (9%)	0.23	1132 (8%)	1282 (9%)	0.04
Valvular heart disease	328 (0.3%)	184 (1.3%)	0.11	129 (1%)	163 (1%)	0.03
PVD	694 (1%)	344 (2%)	0.14	235 (2%)	308 (2%)	0.04
COPD	2286 (2%)	845 (6%)	0.19	675 (5%)	789 (6%)	0.04
Cerebrovascular	2279 (2%)	621 (4%)	0.12	652 (5%)	603 (4%)	0.02
Liver	1016 (1%)	263 (2%)	0.08	213 (2%)	252 (2%)	0.02
Cancer	3868 (4%)	1033 (7%)	0.16	1012 (7%)	997 (7%)	0.005
Undernutrition	1222 (1%)	487 (3%)	0.15	411 (3%)	457 (3%)	0.02
Osteoporosis	3402 (3%)	913 (6%)	0.15	912 (6%)	882 (6%)	0.01

Data are expressed as number (percentage) or mean (standard deviation).
SD: standardized difference; CAD: coronary artery disease; CHD: congestive heart failure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease.

patient-years. To examine the association between AKI and fractures we conducted several analyses. First, we analysed the complete dataset through Cox proportional hazard regression with time to AKI specified as a time-varying exposure. Patients with no AKI served as the referent group and results are expressed as hazard ratio (HR) with 95% CI. Model 1 was univariate analysis, Model 2 included baseline demographics (age, sex, IRSAD, urbanity) and Model 3 included variables associated with risk of AKI and fractures.

Secondly, we used a propensity-matched dataset to balance baseline characteristics between the groups and repeating the analysis. The clinical context of patients with AKI are expected to be different from those without AKI patients, resulting in a high risk of imbalance in baseline characteristics between these groups, many of which could be relevant to fracture risk. A matched propensity cohort should overcome this confounding. Propensity scores were calculated using multivariable logistic regression matching index year of presentation and covariates chosen *a priori* as potential confounders (such as age, sex, presence of comorbidities such as CKD, coronary artery disease, cancer and osteoporosis) and included in each of the propensity score models. Propensity matching used 1:1 optimal matching, caliper 0.1 without replacement. The success of propensity matching was examined by comparing the standardized difference of the covariates, with <0.1 seen as an appropriate matching.

Finally, we conducted a sensitivity analysis using only confirmed AKI status and excluding all patients with unknown AKI. This was undertaken since ICD-10 coding is prone to misclassification and patients who did not have available biochemistry results may have been incorrectly labelled as 'No AKI'. To reduce this measurement bias we a sensitivity analysis including only patients with a known AKI status (baseline creatinine measurement within 365 days) was conducted, thereby excluding all patients with an unknown AKI status. We undertook a subgroup analysis in the sensitivity analysis, dividing the AKI according to severity into Stage 1, 2 or 3 [9] and evaluated the future fracture risk compared with no AKI group.

Analysis was repeated for the complete dataset and the propensity-matched dataset in the sensitivity analysis in addition to a further subgroup analysis using AKI severity status. Potential effect modification of the relationship between fracture and age category, CKD category, sex and known osteoporosis by AKI status was assessed by adding AKI status X tested variable interaction to models. Finally, due to the concerns of potential biases in AKI diagnosis for patients with no previous creatinine measurements, where an improvement in

Table 2: Crude incidence rate of fracture by cohort.

	Fracture number	Follow-up (patient-years)	Incidence rate (per 1000 patient-years)	95% CI
Complete dataset				
All	12 505	513 980	24.3	23.9–24.7
No AKI	11 170	486 839	22.9	22.5–23.4
AKI	1335	27 141	49.2	46.6–51.9
Complete propensity				
All	4015	124 839	32.2	31.2–33.2
No AKI	2696	97 962	27.5	26.5–28.6
AKI	1319	26 877	49.1	46.5–51.8
Sensitivity dataset				
All	9677	317 759	30.5	29.9–31.1
No AKI	8637	296 649	29.1	28.5–29.7
AKI	1040	21 111	49.3	46.4–52.4
Stage I	859	17 191	49.7	46.7–53.4
Stage II	120	2538	47.3	39.5–56.5
Stage III	61	1382	44.1	34.3–56.7
Sensitivity propensity				
All	3322	91 046	36.5	35.3–37.7
No AKI	2283	69 959	31.3	31.2–34.0
AKI	1039	21 087	49.3	46.4–52.4
Stage I	858	17 168	49.9	46.7–53.4
Stage II	120	2538	47.3	39.5–56.5
Stage III	61	1381	44.2	34.4–56.8
Subsidiary				
All	8003	306 487	26.2	25.5–26.7
No AKI	7323	290 833	25.2	24.6–25.8
AKI	680	15 654	43.4	40.3–46.8
Stage I	612	14 102	43.4	40.1–46.9
Stage II	47	1129	41.7	31.3–55.4
Stage III	21	423	49.6	32.4–76.1
Subsidiary propensity				
All	2190	83 507	26.2	25.2–27.3
No AKI	1510	67 859	22.3	22.2–23.4
AKI	680	15 648	43.5	40.3–46.8
Stage I	612	14 096	43.4	40.1–46.9
Stage II	47	1129	41.6	31.3–55.4
Stage III	21	423	49.6	32.4–76.1

creatinine after initial admission was used to diagnose AKI, a subsidiary analysis was performed on the sensitivity dataset. Here patients diagnosed with an AKI without a previous creatinine (group D of our AKI algorithm) (Fig. 1) were excluded from the analysis.

Statistical analysis was preformed using STATA (version 15.1).

RESULTS

Study population

A total of 225 897 patients met our inclusion criteria with our final cohort, after exclusions, consisting of 123 426 individuals with a total follow-up time of 513 980 patient-years (Fig. 2). Our population had more females (57%), a mean age of 53.0 (21.1) years, with most living in a major city compared with a regional area (65% vs 35%). The most common comorbidity at baseline was CKD (6%) and hypertension (9%) with diabetes and coronary artery disease present in 5% and 4%, respectively. Mean follow-up time was 4.2 (2.9) years.

Acute kidney injury

An AKI episode occurred in 14 549 (12%) of patients. During the follow-up period 219 (0.2%) patients were censored for starting dialysis and 11 064 (9%) were censored due to death. Compared with patients who did not have an AKI episode those with an AKI were more likely to be older (mean age 68.8 years vs 50.9 years, $P < .001$), have a background of CKD (22% vs 4%, $P < .001$), hypertension (18% vs 8%, $P < .001$) and diabetes (12% vs 5%, $P < .001$) (Table 1).

Risk of fracture in full dataset

A fracture occurred in 12 505 (10%) patients. In the AKI group 1335 patients developed a fracture compared with the no AKI group of 11 170. The crude incidence of fractures for the full cohort was 24.3 per 1000 patient years (95% CI 23.9–24.7). In the AKI group the crude incidence of fracture was significantly higher when compared with the no AKI group (49.2 vs 22.9 per 1000 patient years, $P < .001$) (Table 2). AKI was a significant risk factor for future risk of bone fracture (HR 1.99, 95% CI 1.88–2.11, $P < .001$) (Fig. 3) with the risk remaining significant

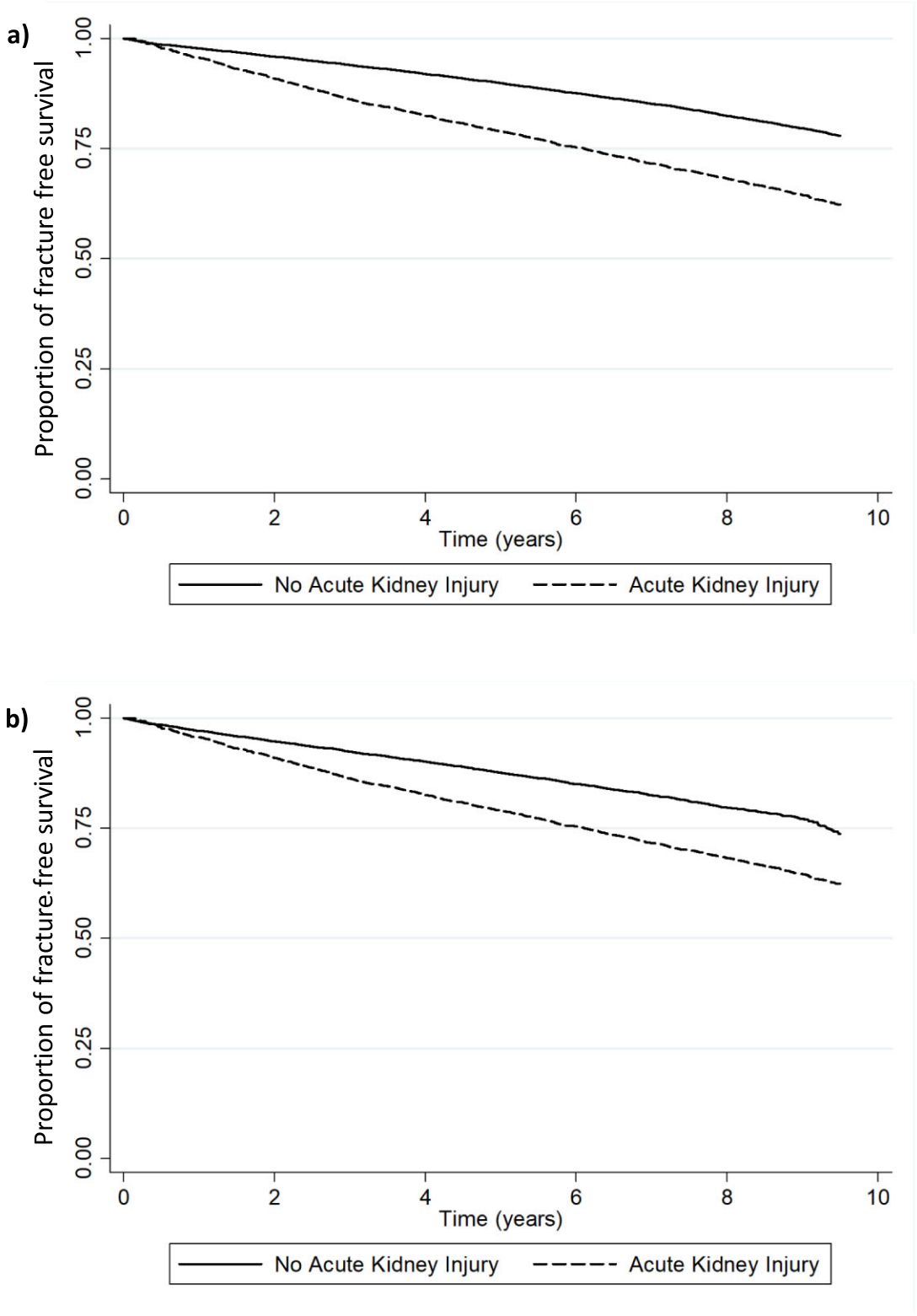

Figure 3: Kaplan–Meier curve showing time to fracture according to AKI in (**a**) complete dataset (**b**) propensity-matched dataset.

Table 3: Risk of fracture following an AKI episode by cohort.

Complete dataset	HR	95% CI	Sensitivity dataset	HR	95% CI	Subsidiary dataset	HR	95% CI
Full cohort			Full cohort			Full cohort		
Model 1	1.99	1.88–2.11	Model 1	1.65	1.55–1.76	Model 1	1.63	1.50–1.76
Model 2	1.59	1.50–1.68	Model 2	1.39	1.37–1.49	Model 2	1.41	1.30–1.53
Model 3	1.50	1.41–1.59	Model 3	1.34	1.25–1.43	Model 3	1.38	1.27–1.49
Propensity			Propensity			Propensity		
Model 1	1.73	1.61–1.86	Model 1	1.47	1.36–1.59	Model 1	1.78	1.62–1.96
Model 2	1.76	1.64–1.89	Model 2	1.46	1.48–1.69	Model 2	1.78	1.61–1.94
Model 3	1.71	1.59–1.83	Model 3	1.44	1.33–1.55	Model 3	1.76	1.59–1.93

Model 1: unadjusted.
Model 2: Model 1 + age, sex, IRSAD, urbanity.
Model 3: Model 2 + CKD, hypertension, diabetes, CAD, CHD, arrythmia, valvular heart disease, PVD, COPD, cerebrovascular disease, liver disease, cancer, undernutrition, osteoporosis.
CAD: coronary artery disease; CHD: congestive heart failure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease.

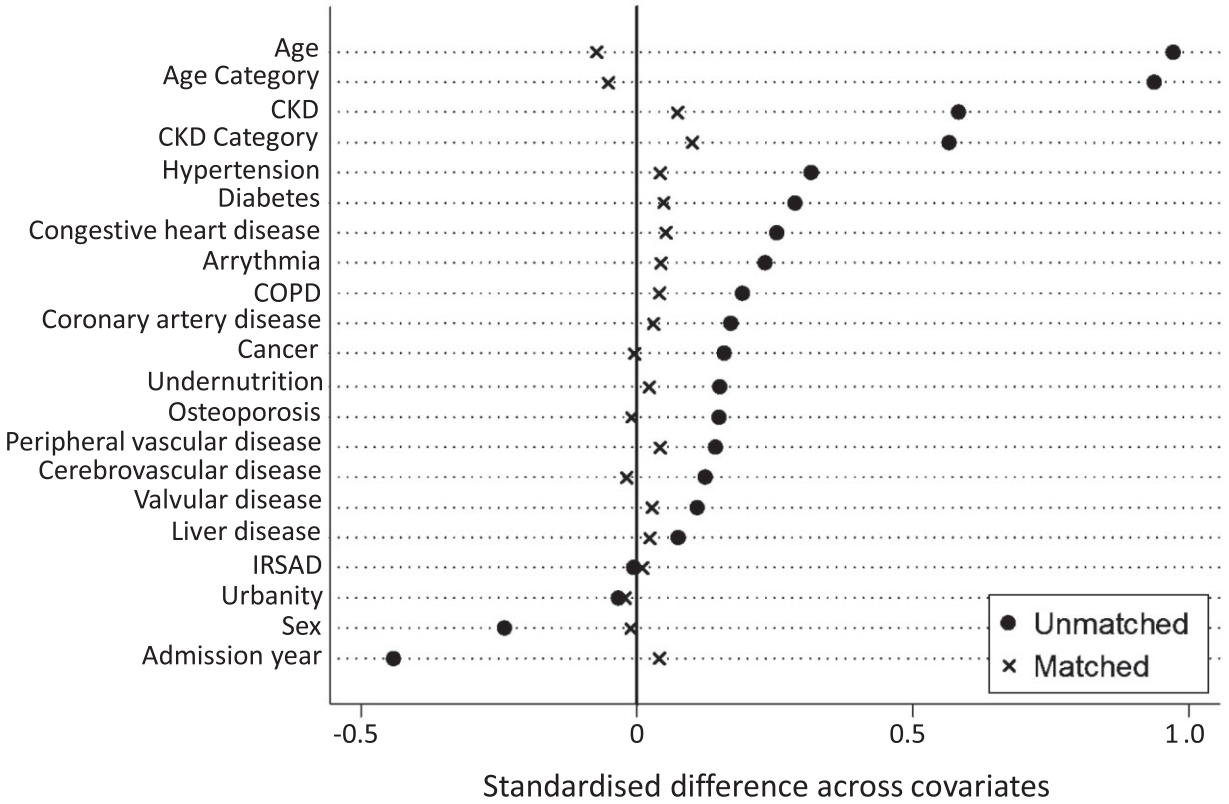

Figure 4: Success of propensity matching. COPD: chronic obstructive pulmonary disease.

in multivariate analysis (HR 1.50, 95% CI 1.41–1.59, $P < .001$) (Table 3).

Risk of fracture in the propensity-matched dataset

We successfully matched 14 362 patients with an AKI with 14 362 patients with no AKI based on propensity score, with a successful balance across patient characteristics (Table 1, Fig. 4). In the propensity-matched dataset, the crude incidence of fracture in the AKI group remained higher per 1000 patient years (49.1, 95% CI 46.5–51.8) compared with the no AKI group (27.5, 95% CI 26.5–28.6). In multivariate models the risk of fracture in the AKI group compared with the no AKI group remained significantly elevated (HR 1.71 95% CI 1.59–1.83, $P < .001$) (Table 3, Fig. 3).

Sensitivity analysis

After excluding patients with no confirmed AKI status, we analysed 70 908 patients with a confirmed AKI history based on their laboratory results (Supplementary data, Fig. S1), of which 10 662 (15%) had an episode of AKI. There were 8163 (12%) patients with AKI stage 1, 1469 (2%) with AKI stage 2 and 1030 (1%) with AKI stage 3. Baseline description for the AKI and no AKI group is provided in Supplementary data, Table S2.

Table 4: Risk of fracture following AKI by subgroup in final model for the complete dataset and the sensitivity dataset.

Complete dataset	HR (95% CI)	P-value	Sensitivity HR 95% CI dataset	P-value
Full cohort			Full cohort	
Sex		.06[a]		.2[a]
Male	1 (Ref)		1 (Ref)	
Female	1.18 (1.14–1.22)		1.39 (1.33–1.45)	
eGFR strata		.9[a]		.2[a]
≥60	1 (Ref)		1 (Ref)	
30-<60	1.14 (1.07–1.22)		1.09 (1.03–1.17)	
<30	1.14 (0.97–1.33)		1.15 (0.99–1.33)	
Age		.04[a]		.07[a]
<30	1 (Ref)		1 (Ref)	
30–50	1.13 (1.06–1.21)		1.28 (1.16–1.41)	
50–70	1.23 (1.15–1.30)		1.44 (1.32–1.57)	
>70	2.39 (2.25–2.54)		3.02 (2.77–3.29)	
Osteoporosis	1.34 (1.18–1.52)	.1[a]	1.47 (1.29–1.67)	.4[a]
AKI stage				.7[b]
1			1.38 (1.28–1.48)	
2			1.32 (1.10–1.58)	
3			1.26 (0.97–1.60)	
Propensity cohort			Propensity cohort	
Sex		<.001[a]		<.001[a]
Male	1 (Ref)		1 (Ref)	
Female	1.61 (1.51–1.72)		1.56 (1.46–1.67)	
eGFR strata		.7[a]		.5[a]
≥60	1 (Ref)		1 (Ref)	
30–<60	1.06 (1.09–1.28)		1.19 (1.09–1.30)	
<30	1.07 (1.03–1.45)		1.16 (0.98–1.36)	
Age		.001[a]		.03[a]
<30	1 (Ref)		1 (Ref)	
30–50	1.27 (0.98–1.63)		1.31 (1.01–1.71)	
50–70	1.38 (1.10–1.74)		1.53 (1.20–1.94)	
>70	2.42 (1.93–3.03)		2.63 (2.07–3.33)	
Osteoporosis	1.48 (1.24–1.77)	.2[a]	1.44 (1.18–1.76)	.9[a]
AKI stage				.7[b]
1			1.44 (1.33–1.57)	
2			1.37 (1.14–1.65)	
3			1.31 (1.01–1.69)	

[a]P-value for interaction.
[b]P-value for significance across AKI stages.

There were 9677 (14%) episodes of fractures, 1040 in patients with an AKI compared with 8637 in patients with no AKI. The risk of fracture following an episode of AKI remained elevated (HR 1.34, 95% CI 1.25–1.43, $P < .001$) in the full dataset for the sensitivity analysis (Table 3, Supplementary data, Fig. S2). However, we did not find an increased fracture risk with increasing stages of AKI in the subgroup analysis (Table 4, Supplementary data, Fig. S3).

We successfully matched 10 644 patients with no AKI episode (Supplementary data, Table S1 and Fig. S4) with 10 644 patients with an AKI episode, out of which 8146 (38%) had AKI Stage 1, 1469 (7%) had AKI Stage 2 and 1029 (5%) had AKI stage 3. Similar to the previous analysis AKI remained an independent risk factor for fractures (Table 3, Supplementary data, Fig. S2), with similar estimates regardless of severity of AKI (Table 4, Supplementary data, Fig. S3).

Subsidiary sensitivity analysis

A subsidiary analysis was preformed using the sensitivity dataset, were only patients with AKI episodes where a previous creatinine measurement was available were included (Fig. 1, excluding group D). In this analysis we excluded 2036 patients in group D and a total of 68 872 patients were included with baseline description for the AKI and no AKI group provided in Supplementary data, Table S2.

The fracture rates and risk of fracture were similar in the subsidiary analysis to the previous analysis (Tables 2 and 3, Supplementary data, Figs S5 and S6) in both the complete dataset and the propensity-matched dataset (Supplementary data, Fig. S7 showing success of propensity matching).

Interaction tests

Interaction tests demonstrated a significant association between sex (in the complete and the sensitivity propensity datasets) and age category (in the complete dataset for the full cohort and in both the complete and the sensitivity propensity datasets) with AKI status and fractures (Table 4), but not CKD stage and osteoporosis. No significance for interaction was seen in the subsidiary analysis (Supplementary data, Table S4). For

Table 5: Relationships between AKI exposure and fracture stratified by sex and age category.

	Fracture							
	Full dataset				Sensitivity			
AKI status	Full cohort, *n* (%)	(*n* = 12 505), HR (95% CI)	Propensity, *n* (%)	(*n* = 4015), HR (95% CI)	Full cohort, *n* (%)	(*n* = 9677), HR (95% CI)	Propensity, *n* (%)	(*n* = 3322), HR (95% CI)
AKI sex								
No								
Female	6712 (54)	1 (Ref)	1632 (41)	1 (Ref)	5286 (55)	1 (Ref)	1371 (41)	1 (Ref)
Male	4458 (36)	0.86 (0.82–0.89)	1064 (27)	0.56 (0.51–0.60)	3351 (35)	0.71 (0.68–0.75)	912 (27)	0.59 (0.54–0.64)
Yes								
Female	744 (6)	1.59 (1.47–1.72)	737 (18)	1.47 (1.34–1.61)	602 (6)	1.32 (1.21–1.44)	601 (18)	1.27 (1.15–1.41)
Male	591 (5)	1.22 (1.12–1.33)	582 (15)	1.14 (1.03–1.26)	438 (5)	1.02 (0.92–1.12)	438 (13)	0.98 (0.88–1.10)
AKI age								
No								
<30	1481 (12)	1 (Ref)	59 (1)	1 (Ref)	590 (6)	1 (Ref)	53 (2)	1 (Ref)
30–<50	2289 (18)	1.12 (1.05–1.19)	150 (4)	1.02 (0.76–1.38)	1231 (13)	1.26 (1.14–1.39)	143 (4)	1.09 (0.79–1.49)
50–70	3068 (25)	1.21 (1.13–1.28)	652 (16)	1.01 (0.77–1.32)	2307 (24)	1.40 (1.28–1.53)	611 (18)	1.21 (0.91–1.61)
>70	4332 (35)	2.37 (2.23–2.52)	1835 (46)	1.75 (1.35–2.27)	4509 (47)	2.99 (2.74–3.26)	1476 (44)	2.05 (1.56–2.70)
Yes								
<30	21 (0.2)	0.87 (0.57–1.34)	21 (0.5)	0.71 (0.43–1.16)	20 (0.2)	0.94 (0.60–1.47)	20 (0.6)	0.72 (0.43–1.21)
30–<50	79 (0.6)	1.54 (1.23–1.94)	79 (2)	1.33 (0.95–1.87)	71 (0.7)	1.69 (1.32–2.17)	71 (2)	1.33 (0.93–1.91)
50–70	364 (3)	1.95 (1.73–2.19)	364 (9)	1.73 (1.31–2.29)	300 (3)	2.14 (1.86–2.47)	300 (9)	1.71 (1.28–2.31)
>70	871 (7)	3.59 (3.28–3.93)	855 (21)	3.07 (2.35–4.01)	649 (7)	3.92 (3.49–4.39)	648 (20)	3.05 (2.29–4.05)

HR represents adjusted HR for the full model.

sex, females were at a higher risk of fracture compared with males in the no AKI group. An AKI exposure increased the risk of fractures, with a larger effect seen in female sex compared with male sex (Table 5, Supplementary data, Table S5). Increasing age was a risk factor for fracture risk, with a similar disproportionate increase in risk of fracture in the AKI group compared with the no AKI group.

DISCUSSION

Using a large population-based cohort covering a 10-year period, we showed that an episode of an AKI, even at milder stages, is a significant risk factor for future bone fractures. To our knowledge this is the first study to examine this association in all patients presenting with AKI, regardless of its severity or hospital setting. We found the effect consistent and preserved across multiple approaches which included propensity matching, to control for confounders, and sensitivity analysis with a *post hoc* analysis, to control for possible AKI misdiagnosis.

CKD is a risk factor for fractures, with the risk increasing as CKD severity progresses [7, 8, 22]. Classical risk factors associated with fractures in the general population are seen in higher proportions in CKD patients such as older age, sex, lower mineral density (osteoporosis/osteopenia) [23], increased inflammation and glucocorticoid therapy [24, 25]. In addition, CKD patients have non-traditional risk factors for fractures manifesting through CKD-MBD. CKD-MBD is a result of disruptions to the normal control of vitamin D, phosphate, calcium, parathyroid hormone and fibroblast growth factor 23 (FGF-23) from impaired kidney function [24, 25]. This in turn leads to abnormalities in bone quality and health from bone turnover disruption, microarchitecture and mechanical properties in addition to a lower bone volume and mineralization [24, 26].

The evidence linking CKD with MBD and the association with an increased risk of fractures is well established, however, similar studies in the AKI population are limited despite evidence that AKI causes disruptions to the normal mineral bone balance. Episodes of AKI results in as much as a 15-fold increase in FGF-23 [27, 28], parathyroid hormone resistance [29, 30] and decreased synthesis of 1,25-dihydroxyvitamin D [28, 31] in the immediate post-AKI period [32]. Klotho, a cytoprotective protein highly expressed in kidneys, also decreases significantly after an AKI episode [32]. Chronic klotho depletion has been associated with low bone turnover and patchy defects in mineralization in mice studies [33, 34]. While these studies tentatively support the link between AKI and a reduction in bone health, we remain limited by the lack of a validated short-term biomarker of bone injury associated with acute or chronic bone health [32]. Similarly, beyond the available limited biomarker measures and examinations, the association between AKI and long-term bone health is poorly studied in the literature. Most of the studies employed animal models and with a limited appreciation on how long the mineral hormonal disruptions (such as elevated FGF-23) persist in humans after an AKI episode. When such biomarkers were examined in the literature following an AKI episode (such as FGF-23 or 1,25-dihydroxyvitamin D) short-term outcomes focused on mortality or need for renal replacement therapy, rather than bone health [28, 31, 35].

No study has examined all AKI episodes on overall mineral bone health including long-term outcomes. One study did examine the association between AKI and the risk of fractures [16], but limited the patient population to AKI patients who required dialysis and recovered. This resulted in a small study population (448 patients), and the results would not be generalizable to all patients with AKI, particularly those with a milder form of AKI who would represent the majority of AKI presentations. Another relevant study is an examination we previously undertook showing an increased risk of kidney stones following an AKI episode [20]. This again, highlights the hypothesis that an AKI episode results in bone mineral balance dysregulation, resulting in long-term clinical outcomes such as an increased risk

of kidney stones. Our current study further adds to this field by showing that long-term clinical outcomes to potential disruptions in the normal mineral balance extends to bone health and a likely increased risk of fractures.

A major strength of our study includes using a large cohort of patients attending a local health district over a 10-year period and being able to capture all hospitalizations and laboratory testing for these patients. We were able to include all creatinine measurements for any emergency, in-hospital admission or outpatient measurements since they were provided by a single laboratory service for the local health district, regardless of the clinical care setting. This allowed us to establish baseline creatinine, determine undiagnosed or undocumented AKI and confirm CKD status. In addition, the large number of patients allowed for successful propensity matching with similar characteristics apart from AKI exposure. Our sensitivity analysis further strengthened our findings by allowing for the inclusion of patients with a confirmed AKI status. A subsidiary sensitivity analysis excluding patients with AKI where a prior creatinine measurement was not available also yielded similar results demonstrating consistency across the cohort, further supporting our conclusions.

Our study does have several limitations. The retrospective nature of our cohort prevents us from proving the direction of causality or the effect of unmeasured confounders. AKI is not a single entity but rather a heterogenous diagnosis with a wide range of aetiologies with complex underlying pathophysiological processes. In addition, AKI is not a static entity or variable, but it does have longitudinal post-AKI outcomes depending on levels of recovery such as complete resolution, recurrent AKI, and progression to acute kidney disease or to CKD. We were not able to account for these in our analysis. Unfortunately, we were not able to account for these in our analysis. Our AKI definition was also dependent on an ICD-10 diagnosis or serum creatinine, and we did not have urine output to assist in the diagnosis. However, such a limitation is inherent to most administrative databases examining AKI. It also has to be acknowledged that our data source is derived from a clinical administrative database and we were unable to account for important variables such as osteoporosis confirmation on DEXA (dual X-ray absorptiometry) scan, body mass index or vitamin D status, which may be relevant to fracture risk. With respect to the outcome, our fracture diagnosis mostly relied on symptomatic hospitalization or admission for management, and while we would anticipate that most fractures would present to hospital for management, we could not ascertain this for all cases. We did not have information on medications which may have influenced fracture outcomes, either as preventative measures (e.g. bisphosphonates and oral vitamin D) or as a risk (e.g. steroids). Our sensitivity analysis was also heavily weight towards the milder AKI stages (Stage 1). While this aligns with expectations and is consistent with those of a hospitalized population, it may not give an accurate reflection for the more severe stages of AKI. This may have been a reason why a dose–response relationship was not seen between the more severe forms of AKI and risk of bone fractures. We therefore caution that our results need to be seen as hypothesis generating with further confirmation in other cohorts and datasets required.

In summary, we showed an increased risk of bone fractures following an AKI episode. Our study contributes novel information to the field, adding to the list of adverse sequelae after an episode of AKI and tying AKI and CKD to BMD. We would recommend further research to confirm these findings in other settings.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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CONFLICT OF INTEREST STATEMENT

None declared.

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