Clinical and Pharmacological Aspects of Hospital-Acquired Acute Kidney Injuries Outside the Intensive Care Unit: A Phenome-Wide Association Study

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Keywords

Acute kidney injury · ICD-10 · Intensive care unit · Phenome-wide association study

Abstract

Introduction: Acute kidney injury (AKI) occurring in the hospital in noncritically ill patients involves a broad spectrum of clinical conditions and medical scenarios that are better appreciated by systematic association studies. **Methods:** We extracted all diagnoses and drug prescriptions from an i2b2 clinical data warehouse for patients who stayed in an academic hospital between 2013 and 2017, and had at least two plasma creatinine measurements performed during the first week of their stay, and analyzed the association between AKI occurring outside the intensive care unit (ICU), as identified using the AKIN classification criteria, and International Classification of Diseases (ICD)-10 diagnosis codes and drug categories. **Results:** 16,662 hospital stays for unique individuals were extracted. The prevalence of AKI outside the ICU was 8%, with a distribution of frequencies that greatly varied according to the departments. 4% of patients with AKI died during their hospital stay (OR 6.17, 95% CI [2.59–17.9]). ICD-

10 diagnosis codes were related to infections, kidney cancer, heart failure, respiratory failure, and chronic kidney disease. Drugs targeting the renin angiotensin system and loop diuretics had the larger size effect on AKI. The ICD-10 code N17/“Acute kidney failure” was recorded in average in only 16% of the cases with AKI, and its frequency ranged from 0 to 80%, according to the hospital department; the lack of encoding did not impact mortality. **Conclusion:** A systematic search for the associations of AKI with prescribed drugs and medical diagnosis using a phenome-wide approach allows to describe in depth the epidemiology of AKI outside the ICU.

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Introduction

Hospital-acquired acute kidney injury (HA-AKI), the abrupt decrease in glomerular filtration rate (GFR) occurring during hospitalization, is a frequent disorder that significantly impacts morbidity and length of stay and leads to the development of chronic kidney disease (CKD) and end-stage renal disease. Since the incidence of HA-

AKI is increasing, its impact on long-term morbidity, death, and cost are likely overlooked, which makes a strong case for improved prevention, recognition, and treatment. The epidemiology and outcomes of HA-AKI have been described in numerous studies, which have in general provided similar results [1–3]. Many of these studies explored the epidemiologic features of HA-AKI occurrence in the setting of intensive care unit (ICU) in critically ill patients, as attested by the high rates of renal replacement therapy and mortality ranging from 20 to 40% [4].

HA-AKI outside the ICU affects a large number of hospitalized patients worldwide and reported frequencies range from 3 to 18% [2–6]. In general, reported risk factors for HA-AKI outside the ICU include older age, male sex, and comorbidities such as diabetes, heart failure, or CKD [4]. Even outside the ICU, AKI is associated with poor outcomes and mortality is typically 10–20% [7]. Despite the high mortality of hospitalized patients with AKI, the reported causes of death are related to coexisting conditions rather than kidney injury, suggesting that additional description of the AKI epidemiology in specific clinical cohorts is useful to better appreciate the spectrum of etiologies and associated medical conditions [8–12]. Inclusive approaches are valuable to better reflect the wide spectrum of clinical scenarios associated with AKI in the hospital and could yield critical cues for preventive strategies and recognition of affected patients. These approaches are made possible through the implementation of clinical data warehouses (CDW) [13, 14] that integrate demographics, vital signs, International Classification of Diseases (ICD)-10 diagnosis codes from the billing system, procedures, clinical data (structured questionnaires from electronic health reports), biological test results, and computerized provider order entry drug prescriptions from all individuals admitted to a hospital [15, 16]. To our knowledge, a comprehensive exploration of all possible diagnoses and drugs associated with HA-AKI occurring outside the ICU has never been performed.

In turn, approaches derived from phenome-wide association studies [17, 18] have emerged as valuable tools for uncovering unexpected associations between factors, such as the whole diagnoses coded using ICD classification, and a qualitative trait (the outcome variable), using multiple testing [19–22]. These comprehensive methods can generate a hierarchical classification of the diagnoses associated with an outcome variable, and several visualization tools have been developed to make these hierarchies easily understandable [23]. In this study, we extracted data from an i2b2 CDW and performed a comprehen-

sive analysis of all the diagnoses and drug prescriptions associated with HA-AKI occurring outside the ICU in a French urban tertiary academic hospital.

Study Population and Methods

Study and CDW

We performed an *in silico* comparative cross-sectional period prevalence survey using data from Georges Pompidou European Hospital in Paris, France. We extracted data from the i2b2 CDW of all individual patients who attended the hospital between 2013 and 2017

Study Population

All first hospital stays of patients (excluding all ICU) between 2013 and 2017 who had data available concerning plasma creatinine measurements during the first 24 h of the admission (baseline creatinine level), and subsequently during the 7 following days in the same department, were included in this study. Patients under chronic hemodialysis were excluded. During this period (Fig. 1), 16,662 non-ICU patients who spend the first week after admission outside ICU departments were included. Each patient was classified according to the presence of AKI. AKI episodes were classified according to the AKIN (Acute Kidney Injury Network) stages [24] and using the relative changes in creatinine level over the 7-day period. Urine output was not used as a criterion for AKI identification. Baseline GFR was estimated using the CKD-EPI formula. Each AKI patient was matched to a non-AKI patient for hospital department, age (age difference lower than 10 years), and baseline GFR (GFR difference lower than 2.5 mL/min/1.73 m²). The final cohort comprised 950 matched case-control pairs of patients.

The international classification of diseases is a medical classification system published by the World Health Organization that contains codes for diseases and health conditions listed in a hierarchical fashion. We extracted for each included stay all ICD-10 codes.

The anatomical therapeutic chemical (ATC) classification system is a drug classification system that classifies the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. The fifth level of the code indicates the chemical substance, for instance “furosemide.” We retrieved for each included stay all prescribed drugs and matched each prescription to the fifth level of the ATC classification system. Chemotherapies were excluded, because of the difficulty to find a homogeneous way to integrate chemotherapies (based on a cycle prescription) with other drug prescriptions (based on a daily prescription). Contrast media drug was also not considered because it is not electronically prescribed.

Statistical Analyses

We measured the strength of the association between each three-digit ICD-10 code (occurring at least in 20 hospital stays) and AKI-matched case-control groups by calculating odds ratios (ORs) and *p* values using McNemar tests. We measured the strength of association between prescribed drugs classified according to the fifth level (prescribed at least in 20 hospital stays) and AKI-matched case-control groups by calculating ORs and *p* values using McNemar tests. We also analyzed the distribution of the

Fig. 1. Flowchart. All hospital stays (16,662), excluding all intensive care units, between 2013 and 2017 with data available regarding plasma creatinine measurements during the first 24 h of the admission (baseline creatinine level), and subsequently during the 7 following days in the same department, were included. AKI was calculated using the AKIN classification. Association studies were performed in a group of patients ($n = 1,900$) who were matched for baseline estimated GFR, hospitalization unit, and age.

code N17/“Acute kidney failure” in the AKI matched case-control groups. We described the distribution of each clinical parameter of interest according to the N17 and AKI status. In the AKI case group, we tested the association between N17 coding and ICD-10 codes systematically by calculating ORs and p values using Fisher’s exact tests.

Data Management

An open database connection linking an Oracle database (11 g Enterprise Edition Release 11.2.0.1.0) of i2b2 CDW (version 1.6)

Table 1. Characteristics of the cohort matched for age, GFR and unit, and AKIN scores

	Cases (AKI+)	Controls (AKI-)	OR/mean difference
Number	950	950	
Age, years	69.1±14.5	69.2±13.9	0.1 ($p = 0.9$)
Charlson score			($p < 0.0001$)
0	108	206	Reference
1–2	297	340	1.6 [1.2–2.2]
3–4	263	208	2.4 [1.8–3.2]
5–6	140	106	2.5 [1.8–3.5]
7 and +	142	90	1.6 [1.1–2.3]
Sex (male)	713 (75.1%)	585 (61.6%)	1.8 [1.5;2.2]
Intrahospital mortality	38 (4%)	7 (0.74%)	6.1 [2.5;18]
AKIN stage			
1 ($n = 805$)	30 (3.7%)		
2 ($n = 38$)	2 (5.3%)		
3 ($n = 107$)	6 (5.6%)		
Length of stay (surviving patients)	11.3 (12.5%)	6.5 (7.7%)	4.8 ($p < 0.0001$)
Mean BMI	26.1 (5%)	25.9 (4.8%)	0.2 ($p = 0.4$)
Baseline GFR	68.3 (22.4%)	68.4 (22.3%)	–0.1 ($p = 0.8$)

to R software (version 3.1.0) was set up. The dataset containing data from the cohort (demographic, creatinine values, ICD-10 codes, and drugs prescribed) was imported into R and analyzed further using the pheatmap and epitools packages. This work adheres to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines [25].

Results

AKI Clinical Risk Factors

In the whole population of patients admitted to the hospital between 2013 and 2017, and who had plasma creatinine measurements during the first 24 h of the admission and subsequently during the 7 following days in the same department, excluding all ICU departments ($n = 1,662$) (Fig. 1), the prevalence of AKI of all AKIN stages was 8%, which is in accordance with the epidemiology of the disease. However, the distribution of AKI frequencies greatly varied according to the hospital departments, from 3% in hypertensive medicine, 8.4% in cardiology, 10.5% in renal medicine, and up to 20% in urology (Fig. 1).

In the AKI-matched case-control groups (Table 1), the Charlson comorbidity index was significantly higher in AKI cases compared with controls, with size effects increasing with morbidity scores, indicating that the risk of developing AKI is higher in patients with multiple comorbid conditions. Male patients developed AKI more frequently than women. AKI occurring outside the ICU

Fig. 2. Distribution of the ICD-10 codes positively associated with AKI in the cohort of 1,900 individuals according to their p values. A total of 143 ICD-10 diagnoses that occurred in at least 20 stays were reported. Multiple comparisons were performed leading to a p value of $(0.05/1,513) = 3.3 \times 10^{-5}$ considered statistically significant after correction for multiple comparisons (Bonferroni). The scatter plot represents the 143 ICD-10 codes significantly ($p < 3.4 \times 10^{-4}$) and positively ($OR > 1$) associated with AKI and classified according to diagnosis families. The red line denotes $p < 3.4 \times 10^{-4}$ and the blue line $p < 0.05$.

Table 2. ICD-10 diagnostic codes associated with AKI

Code	Diagnosis	Cases (AKI+)	Controls (AKI-)	OR [95% CI]
R34	Anuria and oliguria	22	3	7.3 [2.2–38.2]
C64	Malignant neoplasm of the kidney	150	46	6.7 [4.2–11.8]
A41	Sepsis	32	5	6.4 [2.4–21]
B95	<i>Streptococcus</i> and <i>Staphylococcus</i>	30	6	5.8 [2.2–19.2]
R65	Systemic response syndrome	25	5	5 [1.8–17.1]
R57	Shock	56	12	4.6 [2.4–9.5]
Z99	Dependence on renal dialysis	57	17	3.8 [2.1–7.5]
N17	Acute renal failure	171	74	2.8 [2–3.9]
B96	Other bacterial agents	64	25	2.6 [1.6–4.3]
J96	Respiratory failure	72	30	2.5 [1.6–4]
I50	Heart failure	288	170	2.4 [1.9–3.2]
N18	Chronic kidney disease	264	172	2.4 [1.8–3.3]
T81	Complication of procedures	104	60	1.9 [1.3–2.8]
I48	Atrial fibrillation and flutter	270	209	1.5 [1.2–1.9]

Shown are the fourteen 3-digit ICD-10 codes among 143 diagnoses occurring at least in 20 stays, and which were significantly associated with AKI ($p < 3.4 \times 10^{-4}$) after correction for multiple comparison.

seems to be less severe that AKI occurring in the ICU [4], as 4% of patients with AKI died during their hospital stay (OR 6.17, 95% CI [2.59–17.9]), consistent with the fact that a large majority (>80%) of AKI were of low severity (AKIN1). Mortality increased with the severity of AKI. Reflecting the severity of the medical situation associated with AKI, the length of stay was almost twice longer in

patients with AKI compared with those without AKI (median time 11.3 versus 6.5 days; Table 1).

Phenome-Wide Association of the Diagnoses Associated with HA-AKI

We next aimed at determining the medical landscape within which AKI develops, and we analyzed the associa-

tion between each diagnosis and AKI in the case-control matched population. Figure 2 and Table 2 illustrate the distribution of the ORs significantly associated with AKI according to ICD-10 codes after correction for multiple testing ($p < 3.4 \times 10^{-4}$): 14 diagnoses were significantly associated with AKI.

A first category, composed of diagnoses describing the AKI condition, such as N17/“Acute kidney failure,” Z99/“Dependence on renal dialysis,” and R34/“Anuria/oliguria,” mirrors the occurrence of AKI. A second group of diagnoses is composed of A41/“Other causes of sepsis,” B95/“*Streptococcus* and *Staphylococcus*,” R65/“Symptoms and signs specifically associated with systemic inflammation and infection,” R57/“Shock,” B96/“Other bacterial agents as the cause of diseases classified elsewhere,” which indicates that infections and hemodynamic impairment are conditions associated with or promoting AKI. A third diagnosis, C64/“Malignant neoplasm of the kidney,” indicates that surgical procedures of the urinary tract might favor AKI (for example removal of one kidney and transient increase of creatininemia). In line with this, the T81 code/“Complication of procedures (not elsewhere specified)” occurred more frequently in the group of patients with AKI. Finally, codes reflecting baseline comorbidities, such as I50/“Heart failure,” J96/“Respiratory failure,” and N18/“Chronic kidney disease,” likely reflect risk factors for AKI, and corroborate the association of AKI with the high burden of morbidities. The fact that N18/“Chronic kidney disease” is associated with AKI despite adjustment for baseline renal function might reflect inaccuracy in coding strategies, either because CKD is encoded on the basis of an elevated serum creatinine, without taking into account baseline serum creatinine (in fact, AKI), or could be due to a misuse of creatinine-based formula estimating GFR.

The distributions of the frequencies of the occurrence of the diagnostic codes clearly varied according to the hospitalization units, further reflecting the heterogeneity of the medical conditions associated with AKI outside the ICU (Fig. 3). For example, the main diagnosis associated with AKI in urology is related to kidney cancer, reflecting the consequences of partial or total nephrectomies. In general surgery and orthopedics, the most frequently reported diagnoses were related to sepsis and severe infection, which directs to another pathophysiological process. In cardiac surgery and cardiology, the most prevalent diagnoses were atrial fibrillation and flutter and heart failure, potentially leading to hemodynamic instability and renal hypoperfusion. Finally, in renal medicine, the associated diagnoses were acute kidney failure and chron-

Table 3. Drugs associated with AKI

Drug name	Cases (HA-AKI+)	Controls (HA-AKI-)	OR
Magnesium sulfate	25	4	6.2
Ipratropium bromide	44	10	4.7
Furosemide	398	174	4.6
Lansoprazole	74	35	2.7
Heparin	279	141	2.6
Potassium chloride	204	102	2.5
Allopurinol	98	52	2
Insulin	109	62	1.8
Ramipril	169	104	1.8
Carbohydrates	345	237	1.7
Bisoprolol	274	210	1.5

Shown are the 11 drug names among 117 cases in the ATC group 5 occurring at least in 20 stays, and which were found to be significantly associated with AKI ($p < 3.3 \times 10^{-5}$) after correction for multiple comparisons (Bonferroni).

Table 4. N17/“Acute kidney failure” encoding in the matched population, according to the occurrence of AKI

	N17+	N17-	Total	Percentage
AKI-	74	876	950	7.7%
AKI+	171	779	950	18.0%
AKIN1	124	681	805	15.4%
AKIN2	13	25	38	34.2%
AKIN3	34	73	107	31.8%

ic kidney failure, likely reflecting specific renal diseases associated with kidney injuries. Together, these results support the fact that AKI is not a single disease, but a broad clinical syndrome encompassing various etiologies that highly frequently occurs in patients with a high burden of comorbidities, and which is accompanied by a relatively low mortality rate, at least in our cohort.

Drug-Wide Association Study of the Diagnoses Associated with AKI

To determine whether nephrotoxicity could be responsible for AKI outside the ICU, we performed a drug-wide association study to assess the drugs eventually associated with AKI in the matched case-control groups, i.e., for hospital department, age (age difference lower than 10 years), and baseline GFR (GFR difference lower than 2.5 mL/min/1.73 m²). Most drugs positively associated with AKI episodes targeted the cardiovascular system (Table 3), reflecting the high burden of patients with

Fig. 3. Color map of the frequencies of occurrence of the ICD-10 codes associated with AKI according to the hospitalization units. The distribution of the normalized frequencies of occurrence of each ICD-10 code that was significantly associated with AKI after correction for multiple comparisons within each hospitalization unit was mapped.

Table 5. Characteristics of the population of patients with AKI matched for age and baseline

	Cases (AKI+ N17-)	Controls (AKI+ N17+)	OR/mean difference
Number	196	196	
Age, years	74.1±13.9	72.7±13.8	0.1 (<i>p</i> = 0.9)
Charlson score			<i>p</i> = 0.007
0	21	9	
1–2	48	29	
3–4	46	61	
5–6	32	39	
7 and +	22	31	
Sex (male)	119 (70.4%)	121 (71.6%)	0.9 [0.6;1.4]
Intrahospital mortality	4 (2.4%)	25 (14.8%)	7 [2.4;25]
Length of stay (surviving patients)	9.2±6.2	18.4±21.7	9.2 (<i>p</i> < 0.0001)
GFR	59.9±22.4	57.9±5	2 (<i>p</i> = 0.7)
Mortality by unit			
Cardiology	2 out of 73	12 out of 64	0.9 [0.9–1.1]
Cardiac surgery	1 out of 17	2 out of 17	1 [0.8–1.2]
General surgery	0 out of 5	1 out of 10	1 [0.8–1.2]
Gastroenterology	0 out of 0	1 out of 1	0.4 [0.2–0.8]
Orthopedics	0 out of 2	0 out of 1	–
Hypertensive medicine	0 out of 4	0 out of 0	–
Renal medicine	0 out of 10	5 out of 41	Reference
Internal medicine	0 out of 2	0 out of 0	–
Medicine of the elderly	1 out of 5	2 out of 8	0.8 [0.7–1]
Urology	0 out of 51	2 out of 27	1 [0.9–1.1]

cardiovascular diseases, including heart failure, in the population with AKI. Overall, none of the drugs associated with AKI was known to promote nephrotoxicity, but among the drugs with the larger size effect were molecules targeting the renin angiotensin system (such as ramipril, whereas angiotensin receptor blockers did not reach a significant size effect) and loop diuretics, indicating that a proportion of AKI occurring in the population is likely related to renal hypoperfusion (Table 3). Interestingly, potassium perfusions were significantly associated with AKI, possibly reflecting an association with loop diuretics.

Distribution of the ICD-10 N17 Code “Acute Kidney Failure” among Patients with AKI

N17/“Acute kidney failure” was recorded in only 18% (171 out of 950) of the patients with AKI (Table 4). Conversely, patients without AKI were assigned the N17 code in 7.7% (74 out of 950) of the cases. It is possible that these patients were anuric at admission (and therefore coded N17) but without plasma creatinine elevation, or that information on baseline creatinine value was available from external data to the physician, which may have contributed to this observation. The accuracy of N17 coding

seemed to depend on the AKIN class because patients with more severe AKI (AKIN stages 2 and 3) were more often correctly coded as N17 (Table 4), indicating that AKI of low severity (AKIN1) was likely overlooked. In line with this, the mortality and length of stay of correctly encoded patients was higher compared with patients in the AKI case group also but without the N17 ICD-10 code. Notably, the lack of encoding has no impact on the mortality of the patients, whatever the hospital department (Table 5).

Discussion

Our results indicate that a large-scale and systematic phenome- and drug-wide analysis is a valuable approach to produce a comprehensive picture of all the medical situations associated with AKI defined using validated criteria. The prevalence of AKI outside the ICU was 8%, which is in accordance with the reported experience, but the distribution of frequencies greatly varied according to the hospital departments, reflecting the heterogeneity of the medical conditions associated with HA AKI+/ICU-. Moreover, our results are consistent with the notion that

AKI is not a single disease, but a broad clinical syndrome encompassing various etiologies that frequently occur in patients with a high burden of comorbidities [26]. Indeed, we found that the Charlson comorbidity index was significantly higher in patients with AKI compared with controls, and the risk of AKI was positively correlated with the score level. Thus, the Charlson index, which aggregates numerous comorbidities including some which are known as independent risk factors for HA-AKI, such as heart failure, renal disease, or diabetes, appears to be a reliable predictor of AKI outside the ICU.

4% of the patients with AKI died during their hospital stay, and this relatively low mortality rate observed in the study compared with other reports corroborates the high prevalence of AKI of low severity in our cohort. In turn, the low mortality and low severity of AKI episodes may explain why only 16% of patients with AKI were assigned with the corresponding N17 code. Even if subjectivity in N17 coding may occur, favoring distortions between AKI defined by objective criteria (such as AKIN) and the N17 code, this observation underscores the gap that exists between the occurrence of AKI and its translation into the N17 code: either AKI was not identified and diagnosed by the physician and, consequently, not coded, or AKI was diagnosed but considered a medical issue of minor importance and, therefore, not relevant enough to be encoded. Although the rates of N17 encoding greatly varied between hospitalization units, this did not translate into significant variations in mortality rates associated with AKI between units, indicating that coding strategies did not impact mortality.

From a pathophysiological point of view, our observations suggest that a significant proportion of AKI could reflect a functional reduction in glomerular filtration without structural kidney injury ("prerenal azotemia"), which is common in hospital patients, and can be evenly transient. However, this entity is known to carry an independent association with hospital outcomes, notably in terms of mortality, which is a significantly higher compared with those without AKI [5]. This assumption is supported by the findings of the drug-wide association study showing that drugs affecting renal perfusion, such as those targeting the renin-angiotensin system and loop diuretics, have a large size effect on the association with AKI; in turn, no nephrotoxic drugs promoting structural alterations were found. Nevertheless, we identified clinical scenarios and differing etiologies that occur as a complication of severe conditions, in which AKI is likely associated with morbidity, mortality, and long-term complications, such as in patients with sepsis (mostly in

surgery), patients undergoing cardiac surgery and patients with heart failure, or patients with specific renal diseases. In such cases, optimal early recognition and management is warranted to impede morbidity and mortality costs.

Our results should be interpreted while taking into account the limitations inherent to the design of the study. The association study on drugs or nephrotoxic compounds should be interpreted with some caution. First, neither chemotherapies nor contrast media administration were included in this study while they are known to be strongly AKI-associated drugs. The number of plasma creatinine measurements could be positively correlated with the false discovery of AKI, especially in patients with CKD. This association could be a consequence of the technical and biological variability of plasma creatinine measurement results over time in an individual patient. We excluded patients who only had one plasma creatinine measurement performed during the first week following admission because AKI could not be identified in these patients, and their exclusion likely resulted in this study identifying AKI as more common than it is in actuality. The choice to use plasma creatinine at admission as the baseline for identifying AKI (because out-of-hospital baseline creatinine results are not recorded in our electronic medical records) was likely to be associated with some bias, as this criterion may have missed cases of AKI that occurred on admission or overestimated the prevalence of CKD at admission. Finally, because our hospital does not support all medical specialties, some medical situations usually associated with HA-AKI were not sampled, such as liver diseases or pregnancy.

In conclusion, this electronic health report-based exploration of diagnosis-wide and drug-wide associations for AKI has increased our ability to efficiently draw a comprehensive picture of the clinical scenarios which take place in real-life settings. Beyond descriptive analyses, our approach improved our understanding of how complex medical situations associated with AKI will be managed by physicians across different areas of medicine and will allow identifying important areas for progress in AKI prevention and management.

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Statement of Ethics

This study was approved by the Institutional Review Board of the Paris Descartes University.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

C.N. performed analyses, S.J. analyzed the data and wrote the manuscript, N.P. conceived the study, analyzed the data, and wrote the manuscript.

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