Incidence, Outcomes, and Risk Factors of Community-Acquired and Hospital-Acquired Acute Kidney Injury

A Retrospective Cohort Study

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Abstract: The disease burden and outcomes of community-acquired (CA-) and hospital-acquired acute kidney injury (HA-AKI) are not well understood. The aim of the study was to investigate the incidence, outcomes, and risk factors of AKI in a large Taiwanese adult cohort.

This retrospective cohort study examined 734,340 hospital admissions from a group of hospitals within an organization in Taiwan between January 1, 2010 and December 31, 2014. Patients with AKI at discharge were classified as either CA- or HA-AKI based on the RIFLE (risk, injury, failure, loss of function, end stage of kidney disease) classification criteria. Outcomes were in-hospital mortality, dialysis, recovery of renal function, and length of stay. Risks of developing AKI were determined using multivariate logistic regression based on demographic and baseline clinical characteristics and nephrotoxin use before admission.

AKI occurred in 1.68% to 2% hospital discharges among adults without and with preexisting chronic kidney disease (CKD), respectively. The incidence of CA-AKI was 17.25 and HA-AKI was 8.14 per 1000 admissions. The annual rate of CA-AKI increased from 12.43 to 19.96 per 1000 people, but the change in HA-AKI was insignificant. Comparing to CA-AKI, those with HA-AKI had higher levels of in-hospital mortality (26.07% vs 51.58%), mean length of stay (21.25 ± 22.35 vs 35.84 ± 34.62 days), and dialysis during hospitalization (1.45% vs 2.06%). Preexisting systemic diseases, including CKD were associated with increased risks of CA-AKI, and nephrotoxic polypharmacy increased risk of both CA- and HA-AKI.

Patients with HA-AKI had more severe outcomes than patients with CA-AKI, and demonstrated different spectrum of risk factors. Although patients with CA-AKI with better outcomes, the incidence increased over time. It is also clear that optimal preventive and management strategies of HA- and CA-AKI are urgently needed to limit the risks in susceptible individuals.

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Abbreviations: AKI = acute kidney injury, CA-AKI = community-acquired AKI, CGMF = Chang Gung Medical Foundation, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, EMR = electronic medical record, HA-AKI = hospital-acquired AKI, ICD-9 = International Classification of Diseases, Ninth Revision code, LOS = length of stay, NHI = Taiwan National Health Insurance program, RIFLE = risk, injury, failure, loss of kidney function, and end-stage kidney disease, SCr = serum creatinine.

INTRODUCTION

Hospital-acquired acute kidney injury (HA-AKI) is a widely recognized disorder that carries a substantially increased risk of mortality for many hospitalized patients.[1−3] Studies have shown that causes of HA-AKI include sepsis, critical illness, surgery, and use of contrast media and aminoglycosides during hospitalization.[4,5] Few data have been published on the group of patients presenting at hospital with an existing acute increase in serum creatinine (SCr) level, or community-acquired AKI (CA-AKI).[6−11] Studies have reported that the incidence of CA-AKI was 2 to 3 times higher than HA-AKI,[8,10] but has the same prognostic significance as HA-AKI on mortality, longer length of stay (LOS) and higher healthcare costs.[1,8,10]

Recent literature reviews have suggested that there are etiological and geographical differences in characteristics of AKI in different regions of the world.[12,13] For instance, in some countries, CA-AKI is more likely to be associated with chronic kidney disease (CKD), other chronic disease conditions (liver, heart, lung),[8,10,14] and polypharmacy with nephrotoxic drugs.[15] In other countries, CA-AKI occurs most frequently in young, previously healthy individuals or in the context of one particular predisposing disease.[13] More information on the burden and consequences of AKI will therefore facilitate better prevention and management.

A set of criteria for analyzing the severity of AKI, known as RIFLE (risk, injury, failure, loss of function, end stage of kidney disease), has been widely adopted. It has been used to flag the likelihood of developing AKI, particularly CA-AKI,[16] but its utility in a Taiwanese adult cohort is less clear. CKD and dialysis are widespread in Taiwan, so it is important to characterize variability in risk among groups of patients, to facilitate early identification and prevention of disease. The aim of this

study is therefore to investigate the incidence, severity, and outcomes of AKI in Taiwan. We also examined the potential risk factors for AKI associated with hospital admission in a large adult cohort.

METHODS

The study was approved by the Institutional Review Board and the Ethics Committee of Chang Gung Medical Foundation (CGMF), Taiyuan, Taiwan.

Study Design, Setting, and Sources of Data

The cohort study was conducted using electronic medical records (EMRs) for the period from January 1, 2010 to December 31, 2014 from CGMF. CGMF is the largest group of hospitals within an organization in Taiwan, and in 2013, it provided approximately 11% of the total Taiwan National Health Insurance (NHI) program-reimbursed healthcare services, including emergency, outpatient, and inpatient care.[17] The Taiwan NHI program is a compulsory, nationwide health insurance program, which covers more than 95% of contracted hospitals in Taiwan and 99% of the 23 million persons enrolled in the program.[18] CGMF maintains comprehensive, centralized patient-level EMRs for the hospitals located from the North to South of Taiwan, so the study participants are considered generalizable to the Taiwan general population.

AKI Cohort

The study included all patients hospitalized between January 1, 2010 and December 31, 2014 with a discharge diagnosis of International Classification of Diseases, Ninth Revision (ICD-9) code of 584, for AKI. The first admission for AKI during the study period was defined as the index admission. AKI events were further categorized by RIFLE (risk, injury, failure, loss of function, and end stage) stage (risk, injury and failure) according to the ratio 1.5 to 2.0, 2.0 to 3.0, and >3.0.[16] When the index SCr at admission was 4.0 mg/dL or more, the episode was categorized as failure stage. Using 2 methods to identify the presence of AKI, ICD-9 codes for discharge diagnosis and the RIFLE (risk, injury, failure, loss, and end-stage kidney disease) definition, provided additional confirmation of a correct diagnosis. Patients diagnosed as AKI by a discharge diagnosis of AKI but not met with RIFLE classification stage 1 criteria were classified as non-RIFLE AKI group.

SCr laboratory evaluations at index admission, previous year (baseline) and during hospitalization were examined. For CA-AKI, baseline SCr was defined as the lowest measured SCr within the 12 months before the index SCr at admission.[19] If there was more than one laboratory result in the baseline period, the lowest value was used. For CA-AKI, only index SCr performed in the emergency department of outpatient clinic of the patient's hospitalization were included to classify as CA-AKI related hospitalization. The HA-AKI group of patients was those for whom the highest measured SCr during hospitalization increased at least 1.5 times above admission value (peak/index SCr ≥ 1.5). Patients who met the criteria of CA-AKI were excluded from the assessment of AKI developed during hospitalization.

Only patients aged ≥18 years at index admission were enrolled in the study. Exclusion criteria included patients who had undergone renal replacement therapy, including dialysis or renal transplant, within 12 months before the index admission, and absence of valid SCr laboratory results at index, baseline, and at least one follow-up point.

Outcomes

The incidence of AKI was calculated by dividing the number of cases by the total number of hospitalizations in each calendar year. Patient-level outcomes included mortality, LOS, and dialysis during the index hospital admission. Recovery of renal function at the time of discharge was classified by eGFR improvement ≥50% (≥1.5-fold reduction from the index eGFR) or ≥60 mL/min/1.73 m^2. The measure of eGFR was based on the Modification of Diet in Renal Disease equation, which is routinely used in the study setting.

Baseline Risk Factor Assessment

Demographic information, clinical condition, and medical history for the 12 months before the index admission were retrieved for all study patients. Quan–Charlson comorbidity Index score[20] was used to categorize degree of severity of baseline clinical conditions. Information about use of medicines concerned in patients with impaired renal function was retrieved from the outpatient pharmacy dispensing records for all study patients. Exposure to medicines with nephrotoxic potential initially was defined as ever/never use of study drugs within the 3-month risk window before admission.[15] In a second step, cumulative exposure was identified by the sum of all types of different nephrotoxic medicines identified within the 3-month risk window.[21] Medication uses with renal dysfunction concerns (Supplemental Table 1, http://links.lww.com/MD/A966) were categorized into 19 classes by pharmacological mechanism[22] and modified using the potentially inappropriate medication list for the elderly in Taiwan.[23]

Statistical Analysis

Continuous data are presented as mean (standard deviation, SD) or median (interquartile range, IQR, 25th–75th percentile), and categorical data as number and percentages. Means of baseline characteristics were compared using unpaired Student t tests for continuous variables and Chi-square tests for categorical variables. To identify any trends in incidence of CA- and HA-AKI, annual changes over the study period were examined using the Cochran–Armitage test for binomial outcome.[24] A primary multivariate logistic regression model was employed to determine the ORs and 95% confidence intervals (CIs) to predict the occurrence of AKI based on all baseline characteristics. A secondary multivariate logistic regression model was used to identify the OR for developing CA- or HA-AKI based on all baseline characteristics. All analyses were carried out using SAS version 5.1 (Stata Corp, College Station, TX).

RESULTS

The study cohort included 395,219 adults with a total of 734,340 hospitalizations between January 1, 2010 and December 31, 2014. The average age at admission was 57.48 (±17.25) years old and 64.7% were male patients. The mean LOS was 11.90 (±19.63) days.

Incidence of AKI

During 2010 to 2014, 14,684 (2%) hospital discharges with a diagnosis of AKI were identified, using the International Classification of Diseases Version 9 (ICD9-CM), code 584. The overall AKI-associated hospitalization was 20.21 per 1000 admissions (±0.97). The incidence of AKI according to the RIFLE definition complicated with 11,542 patients, of whom there were 6,287 with CA-AKI (17.25 ± 3.86 per 1000 people),
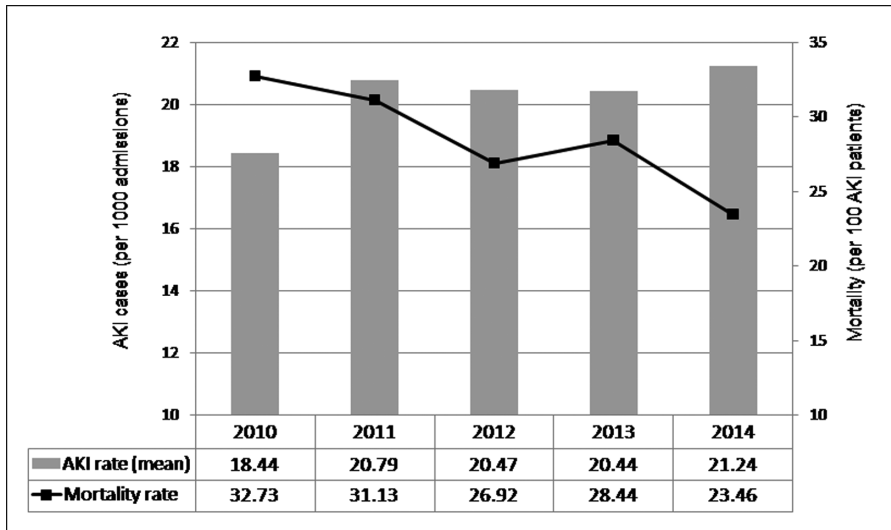
FIGURE 1. Incidence of discharges with a diagnosis of AKI and mortality rate, 2010–2014; AKI = acute kidney injury.

3104 with HA-AKI (8.14 ± 1.68 per 1000 people), and 2151 with non-RIFLE AKI (5.76 ± 1.35 per 1000 people). The agreement on the presence of AKI between disease codes and the RIFLE definition was 81.36% [(6287 + 3104)/ 11,542] among patients with more than 2 SCr measures. Excluding patients with baseline CKD (n = 2568 admissions, 17.5%), from the study cohort, the rate of AKI was 1.68% hospital discharges.
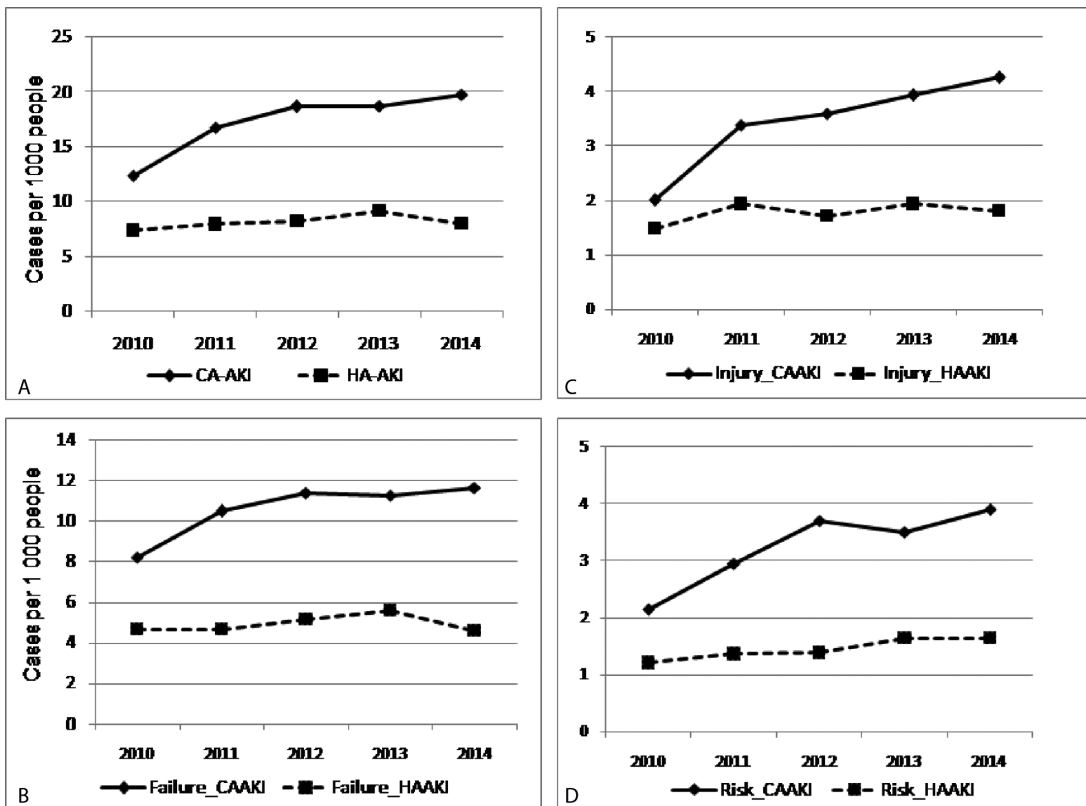

FIGURE 2. Incidence rate of RIFLE-based AKI, by calendar year and severity. Data are presented as mean cases per 1000 hospitalized adults. AKI = acute kidney injury, CA-AKI = community-acquired AKI, HA-AKI = hospital-acquired AKI, RIFLE = risk, injury, failure, loss of function, and end stage of renal disease.

Changes in Trends in AKI Incidence

Over the study period, the annual rate of discharge with a diagnosis of AKI increased from 18.44 to 21.24 cases per 1000 admissions (Figure 1). The annual rate (mean) among patients with CA-AKI increased over time (from 12.35 to 19.76 cases per 1000 people) ($P < 0.0001$), but the change in HA-AKI was insignificant (from 7.36 to 8.02 cases per 1000 people) ($P = 0.10$) (Figure 2A). The difference in annual trend between the 2 was significant ($Z = 4.5268$, 1-sided $P < 0.0001$). Figure 2B–D shows the changes in rate over time by RIFLE stages. The annual rate (mean) for the failure stage was high for both HA- and CA-AKI, and increased over time in CA-AKI (from 8.2 to 11.62 per 1000 people) (Figure 2B). The annual rate for the risk stage was low, but increased in both groups (HA from 1.20 to 1.63 cases and CA from 2.15 to 3.89 cases per 1000 people) (Figure 2D). There was an increase in the injury stage in CA-AKI (from 2.0 to 4.25 cases per 1000 people), but no change in HA-AKI (Figure 2C).

Table 1 shows the baseline characteristics of patients by RIFLE definition of AKI. There were consistently more male patients in all groups, in a ratio of 3:2. On average, patients were 68.02 (± 15.33) years old for CA-AKI, 66.61 (± 16.23) for HA-AKI, and 68.37 (± 16.24) for non-RIFLE AKI. Patients in the CA-AKI group generally had more Quan–Charlson comorbid conditions than other groups. The most common preexisting comorbid conditions among patients with AKI were diabetes with/without complications (34.01%), CKD (17.67%), and tumors, including metastatic solid tumors (23.27%).

AKI Outcomes

In-Hospital Mortality

The overall in-hospital mortality was 30.71% in patients with AKI diagnosis at discharge, compared with 3.33% for patients without AKI. The annual mortality rate associated with AKI steadily declined from 32.73% in 2010 to 23.46% in 2014

TABLE 1. Demographic and Clinical Characteristics of Study Cohort by Type of AKI

	Overall (n = 11,542)	CA-AKI (n = 6287)	HA-AKI (n = 3104)	Non-RIFLE AKI (n = 2151)	P
Gender, n, %					<0.0001
Male	6985 (60.52)	3688 (58.66)	2021 (65.11)	1276 (59.32)	
Age, y	67.7 ± 15.76	68.02 ± 15.33	66.61 ± 16.23	68.37 ± 16.24	<0.0001*
Age, y					<0.0001
18 to <30	244 (2.11)	106 (1.69)	84 (2.71)	54 (2.51)	
30 to <45	825 (7.15)	426 (6.78)	243 (7.83)	156 (7.25)	
45 to <60	2352 (20.38)	1266 (20.14)	685 (22.07)	401 (18.64)	
60 to <75	3709 (32.13)	2086 (33.18)	973 (31.35)	650 (30.22)	
≥75	4412 (38.23)	2403 (38.22)	1119 (36.05)	890 (41.38)	
Quan–CCI score	1.72 ± 1.86	2.08 ± 1.94	1.31 ± 1.67	1.24 ± 1.61	<0.0001
MI	159 (1.38)	110 (1.75)	26 (0.84)	23 (1.07)	
CHF	640 (5.54)	430 (6.84)	117 (3.77)	93 (4.32)	
Peripheral vascular disease	149 (1.29)	107 (1.7)	34 (1.1)	8 (0.37)	
CVD	1017 (8.81)	677 (10.77)	197 (6.35)	143 (6.65)	
Dementia	313 (2.71)	214 (3.4)	51 (1.64)	48 (2.23)	
CPD	799 (6.92)	496 (7.89)	191 (6.15)	112 (5.21)	
Rheumatologic disease	107 (0.93)	72 (1.15)	25 (0.81)	10 (0.46)	
Peptic ulcer bleeding	937 (8.12)	650 (10.34)	171 (5.51)	116 (5.39)	
Liver diseases	1131 (9.80)	817 (13.0)	205 (6.60)	109 (5.07)	
DM without complications	3201 (27.73)	2035 (32.37)	653 (21.04)	513 (23.85)	
DM with complications	725 (6.28)	560 (8.91)	85 (2.74)	80 (3.72)	
Hemiplegia or paraplegia	42 (0.36)	28 (0.45)	7 (0.23)	7 (0.33)	
CKD	2039 (17.67)	1369 (21.78)	390 (12.56)	280 (13.02)	
Tumors	2686 (23.27)	1643 (26.13)	685 (22.07)	358 (16.64)	
HIV/AIDS	4 (0.03)	4 (0.06)	0	0	
Prior nephrotoxic medicine use					
None	3658 (31.69)	1758 (27.96)	1115 (35.92)	785 (36.49)	<0.0001
1 to <3 categories	3200 (27.72)	1603 (25.5)	907 (29.22)	690 (32.08)	
≥3 categories	4684 (40.58)	2926 (46.54)	1082 (34.86)	676 (31.43)	
Number of drug categories	2.19 ± 2.08	2.43 ± 2.13	1.96 ± 2.04	1.79 ± 1.91	<0.0001

Data are shown as the mean (standard deviation, SD) for age and Quan–CCI (Quan–Charlson Comorbidity Index) score, and number of nephrotoxic drug categories, and number (percent of group) of patients in each group.

Liver diseases include mild, moderate, and severe; tumors include any malignancy and metastatic solid tumor.

AKI = acute kidney injury, CA-AKI = community-acquired AKI, CHF = congestive heart failure, CKD = chronic kidney disease, CPD = chronic pulmonary disease, CVD = cerebrovascular disease, DM = diabetes mellitus, HA-AKI = hospital-acquired AKI, HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome, MI = myocardial infarction, non-RIFLE AKI = patients discharged with a diagnosis of AKI but not meeting the RIFLE criteria (i.e., SCr changes < 1.5 times), RIFLE = risk injury failure loss and end stage of renal disease.

*P-value calculated using ANOVA.

TABLE 2. Patient Outcomes

	Overall (n = 11,542)	CA-AKI (n = 6287)	HA-AKI (n = 3104)	Non-RIFLE AKI (n = 2151)	P
In-hospital mortality, n (%)	3545 (30.71)	1639 (26.07)	1601 (51.58)	305 (14.18)	<0.0001
Length of stay (days)	25.2 ± 26.65	21.25 ± 22.35	35.84 ± 34.62	21.38 ± 19.99	<0.0001
Dialysis during hospitalization, n (%)	166 (1.44)	91 (1.45)	64 (2.06)	11 (0.51)	<0.001

Data are shown as the mean (± standard deviation, SD) for length of stay, and number (percent of group) of patients in each group.

AKI = acute kidney injury diagnosis at discharge, CA-AKI = community-acquired AKI, HA-AKI = hospital-acquired AKI, non-RIFLE AKI = patients with a diagnosis of AKI at discharge but not meeting the RIFLE criteria (i.e., SCr changes < 1.5 times), RIFLE = risk injury failure loss and end stage of renal disease.

(Figure 1). The mortality rate was higher in patients with HA-AKI (51.58%) than CA-AKI (26.07%) or non-RIFLE AKI (14.18%) ($P < 0.0001$). Table 2 presents the outcomes among patients with AKI. On average, the LOS was longer for HA-AKI (35.84 ± 34.62 days) than CA-AKI (21.25 ± 22.35 days) or non-RIFLE AKI (21.38 ± 19.99 days). In total, 166 patients (1.44%) received dialysis during hospitalization. The percentage of the group requiring dialysis was larger for HA-AKI (2.06%) than CA-AKI (1.45%) or non-RIFLE AKI (0.51%) ($P < 0.001$). Detailed outcomes among patients with and without AKI, and by severity of RIFLE AKI are shown in Supplemental Table 2, http://links.lww.com/MD/A966.

Renal Outcomes

Patients with CA-AKI had worse renal function at admission than patients with HA-AKI or non-RIFLE AKI. They had a higher SCr value at admission (4.66 ± 3.63 vs 2.56 ± 2.66 for HA-AKI), and a lower estimated glomerular filtration rate (eGFR) level (21.56 ± 20.29 vs 55.26 ± 51.36). The severity of AKI was not significantly different between HA- and CA-AKI groups ($P = 0.14$).

The frequency of renal recovery upon discharge (eGFR return at least 50%) was higher in non-RIFLE AKI (49.5%) than HA-AKI (16.08%), and CA-AKI (57.15%) ($P < 0.0001$). More patients with non-RIFLE AKI (49.39%) had a final measure of eGFR ≥ 60 mL/min/1.73 m^2 than CA-AKI (24.34%) or HA-AKI (15.06%) ($P < 0.0001$) (Table 3).

Risk Factors Associated With RIFLE AKI

Figure 3 shows the odds ratios (ORs) associated with developing RIFLE-AKI. In the multivariate regression analysis, the independent risk factors associated with CA-AKI (vs non-RIFLE AKI) included many comorbid conditions and prior use of nephrotoxic medicines (adjusted odds ratio [aOR], 1.05; 95% CI, 1.02 − 1.08) (Figure 3A). Being male (aOR, 1.22; 95% CI, 1.08 − 1.37), using nephrotoxic medicines (aOR, 1.07; 95% CI,

TABLE 3. Severity of AKI and Recovery of Renal Function

Renal Function at Admission	Overall (n = 11,542)	CA-AKI (n = 6287)	HA-AKI (n = 3104)	Non-RIFLE AKI (n = 2151)	P
SCr (mg/dL)[*]	3.58 ± 3.26	4.66 ± 3.63	2.56 ± 2.66	1.92 ± 0.85	<0.0001
eGFR (mL/min/1.73 m^2)[†]	34.32 ± 35.75	21.56 ± 20.29	55.26 ± 51.36	41.38 ± 26.26	<0.0001
eGFR ≥ 60 (mL/min/1.73 m^2)	1818 (15.75)	276 (4.39)	1181 (38.05)	361 (16.78)	<0.0001
RIFLE stage					0.14[‡]
Risk	1719 (18.3)	1174 (18.67)	545 (17.56)	NA	
Injury	1896 (20.19)	1237 (19.68)	659 (21.23)	NA	
Failure	5776 (61.51)	3876 (61.65)	1900 (61.21)	NA	

Renal Function at Discharge	Overall (n = 9199)	CA-AKI (n = 4429)	HA-AKI (n = 2954)	Non-RIFLE AKI (n = 1816)	P
Last SCr (mg/dL)	2.94 ± 2.55	3.25 ± 2.79	3.45 ± 2.5	1.36 ± 0.85	<0.0001
eGFR ≥ 60 (mL/min/1.73 m^2)	2420 (26.31)	1078 (24.34)	445 (15.06)	897 (49.39)	<0.0001
eGFR recovery ≥ 50%	2414 (26.24)	2531 (57.15)	475 (16.08)	899 (49.5)	<0.0001

Data are shown as the mean (± standard deviation, SD) for length of stay, and number (percent of group) of patients in each group; renal function recovery was defined using the last eGFR measure during hospitalization, as the presence of eGFR ≥ 60 mL/min/1.73 m^2, or return to at least 50% of index value (at admission).

AKI = acute kidney injury, CA-AKI = community-acquired acute kidney injury, eGFR = estimated glomerular filtration rate, HA-AKI = hospital-acquired acute kidney injury, NA = not applicable, non-RIFLE AKI = patients discharged with a diagnosis of AKI but not meeting the RIFLE criteria (i.e., SCr changes < 1.5 times), RIFLE = risk injury failure loss and end stage of renal disease, SCr = serum creatinine.

[*]SCr at baseline (median, 25th−75th quartile): CA-AKI: 3.66 (2.01−6.10); HA-AKI: 1.43 (0.9−3.27); non-RIFLE AKI: 1.70 (1.28−2.48).

[†]eGFR at baseline (median, 25th−75th quartile): CA-AKI: 14.76 (8.04−29.79); HA-AKI: 45.34 (16.64−78.56); non-RIFLE AKI: 35.82 (22.65−50.96).

[‡]P-value calculated using Chi-square test for CA- and HA-AKI.
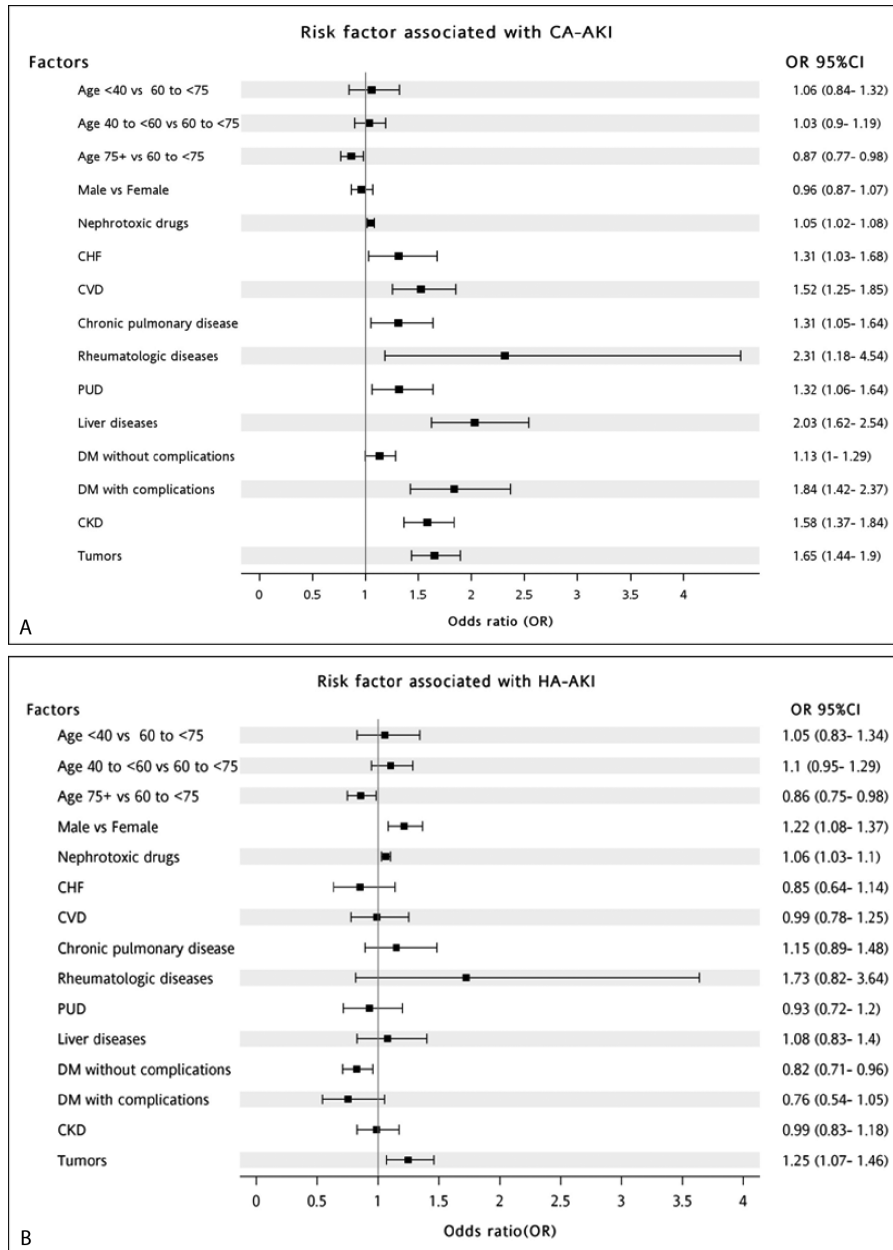
FIGURE 3. Risk factors associated with RIFLE-AKI. (A) CA-AKI vs non-RIFLE AKI. (B) HA-AKI vs non-RIFLE AKI. AKI = acute kidney injury, CA-AKI = community-acquired AKI, CHF = congestive heart failure, CI = confidence interval, CKD = chronic kidney disease, CVD = cerebrovascular disease, DM = diabetes mellitus, HA-AKI = hospital-acquired AKI, non-RIFLE AKI = patients with a discharge diagnosis of AKI but not meeting the RIFLE criteria (i.e., SCr changes < 1.5 times), OR = odds ratio, PUD = peptic ulcer disease, RIFLE = risk injury failure loss and end stage of renal disease. Liver diseases include mild, moderate, and severe; tumors include any malignancy and metastatic solid tumor.

$1.03-1.10$) and having a cancer history (aOR, 1.25; 95% CI, $1.07-1.46$) were associated with an increased risk of developing HA-AKI (Figure 3B).

More than 70% of AKI patients had used at least one prescription with renal dysfunction concern before developing AKI (72.04% for CA-AKI, 64.08% for HA-AKI, and 63.51% for non-RIFLE AKI). The proportion of patients exposed to more nephrotoxic medicines was higher for CA- than HA-AKI (Cochran–Armitage test, $Z = 10.94$, 1-sided $P < 0.0001$)

(Figure 4A); baseline renal function was worse in the CA-AKI group (Table 2). We also examined the association between number of nephrotoxic medicines and AKI severity. Figure 4B shows the distribution of number of nephrotoxic medicines previously used by RIFLE stages. Compared with patients at the risk stage of AKI, those who were exposed to more types of nephrotoxic medication before admission were more likely to develop severe stage AKI (Cochran–Armitage test supports the trend, $Z = -6.52$, 1-sided $P < 0.001$). The
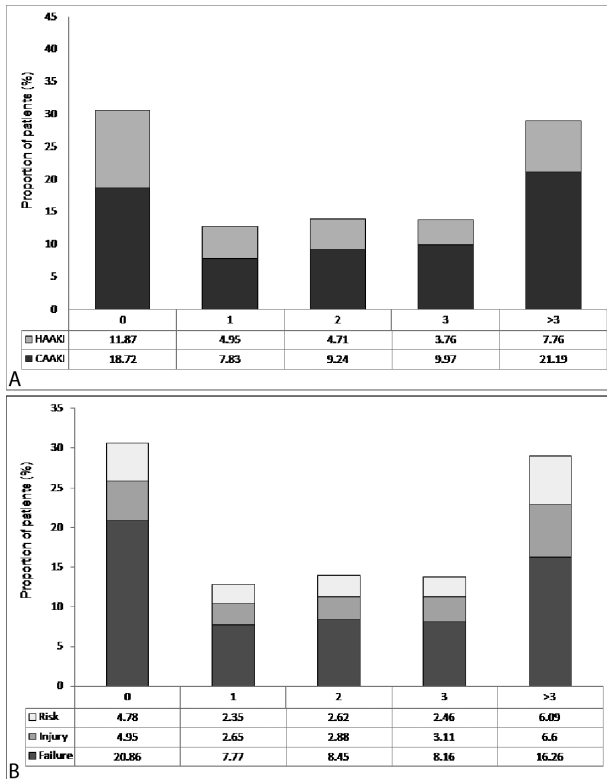
FIGURE 4. Prior uses of nephrotoxic medicines in patients with RIFLE AKI. (A) Number of nephrotoxic medicines, by CA- and HA-AKI; Cochran–Armitage test suggests that the probability of CA-AKI increases with nephrotoxic polypharmacy ($Z = 10.94$, 1-sided $P < 0.0001$). (B) Number of nephrotoxic medicines by severity of RIFLE stages; Cochran–Armitage test for failure (vs risk stage), $Z = -6.52$, 1-sided $P < 0.0001$; Cochran–Armitage test for injury (vs risk stage), $Z = 0.70$, 1-sided $P = 0.24$. CA-AKI = community-acquired acute kidney injury, HA-AKI = hospital-acquired AKI, non-RIFLE AKI = patients discharged with a diagnosis of AKI but not meeting the RIFLE criteria (i.e., SCr changes < 1.5 times), RIFLE = risk injury failure loss of function and end stage of renal disease.

association between number of drug categories used and the injury stage was not significant (Cochran–Armitage test supports the trend, $Z = 0.70$, 1-sided $P = 0.24$). The most common nephrotoxic medicines used before AKI admission were antihypertension agents (e.g., aldosterone antagonists, angiotensin II-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers), antithrombotic agents, and nonsteroid antiinflammatory drugs (NSAIDs) (see Supplemental Table 1, http://links.lww.com/MD/A966).

DISCUSSION

This large, cohort study of hospitalized adults confirmed the findings from previous studies in different practice settings that CA-AKI was more common than HA-AKI.[8,10,25] Both CA- and HA-AKI increased risk of mortality, but in-hospital mortality and LOS were worse in HA-AKI than CA-AKI.[8,10,25] One of the major findings of this study was that CA-AKI increased steadily over time,[12,26] which suggests that it could have a significant impact on the quality of patient care and healthcare resource utilization.

The study results demonstrated that the risk profile was different for CA- and HA-AKI, with CA-AKI being more common in patients with preexisting chronic diseases, including diabetes, rheumatologic diseases, CKD, liver disease, chronic pulmonary disease, peptic ulcer disease, cerebrovascular disease, congestive heart failure, and tumor (Figure 3). In contrast, baseline comorbid conditions were not linked to HA-AKI, indicating that the causes and etiology of AKI developed during hospitalization differed from those in patients admitted with existing renal dysfunction. Several single-setting studies have reported that prevalence of HA-AKI varied by inpatient setting (e.g., medical or surgical wards, and intensive care) and was linked to common hospital-related factors including heart failure, sepsis, cardiac catheterization, use of aminoglycosides and radiographic contrast media and acute organ system dysfunction.[27–30] The distribution of common discharge diagnoses was broad and varied between patients with CA- and HA-AKI (Supplemental Table 3, http://links.lww.com/MD/A966). It is possible that health professionals are now more aware of AKI in hospitalized patients, as the decline in in-hospital mortality in this study was consistent with previous results.[14,31]

The medicines should be used with caution in patients with impaired renal function was prevalent in the study cohort. Prior target medications exposure was linked to both CA- and HA-AKI, after adjusting for patient demographic characteristics and preexisting chronic conditions. Exposure to more nephrotoxic medicines was associated with more severe AKI. The impact of prior polypharmacy with nephrotoxic drugs on AKI development has also been highlighted in recent observational studies.[15,32] One study using RIFLE criteria in a population-based case–control study suggested that NSAIDs used in combination with rennin–angiotensin system inhibitors (RASIs) and/or diuretics increased the risk of CA-AKI by 64%.[15] We found that NSAIDs, RASIs, and diuretics were used frequently in the three months before admission for CA-AKI, which is consistent with a complex background of chronic conditions in the study cohort, and suggests these patients were likely to have unstable or severely impaired renal function.

The agreement on presence of AKI between diagnostic code at discharge and SCr changes in the study was considered high (82%) among patients with more than 2 SCr measures. A large discharge cohort study suggested that using hospital discharge code would lead to substantial underestimation of AKI incidence, as milder changes or rapidly reversible SCr results may not be coded as AKI.[33] RIFLE classification, however, relies on having at least 2 measures of renal function, which depends on the frequency of SCr testing in the relevant practice setting. AKI may therefore go undetected because of insufficient SCr testing. As the diagnostic code is unable to differentiate severity of kidney injury, greater RIFLE AKI severity revealed a link to higher mortality and longer LOS, which showed good discrimination for patient outcomes of the RIFLE stages in the study cohort. The 18% of patients who had an AKI discharge code but did not reach the threshold for RIFLE classification had a higher risk of mortality than patients without AKI, indicating that a single measure of SCr may be insufficient to reflect clinical responses. Further research including urine output or more sensitive biomarkers of renal injury may improve accurate identification of AKI.[34]

The major strength of this study is the availability of SCr laboratory results from a large cohort of hospitalized adults, which allowed us to use the up-to-date consensus RIFLE criteria to identify AKI, in particular CA-AKI, and to differentiate degrees of severity of AKI in the study cohort. The differences

in comorbid conditions, prior nephrotoxic polypharmacy and baseline SCr level between HA- and CA-AKI will help to identify patients who are particularly vulnerable to different forms of AKI. The study results also revealed new information about trends in HA- and CA-AKI, supporting development of strategies to limit the risks of CA-AKI.

The study did, however, have some limitations. First, although possible misdiagnosis of AKI (ICD-9-CM codes have a positive predictive value of 47.9% for AKI)[33] was avoided by using the RIFLE definitions, the true incidence of AKI may be underestimated. The baseline incidence of RIFLE AKI that does not result in hospitalization is unknown. Patients with a spuriously high or low SCr value may have received a misclassification of AKI incidence or severity stage. This study was performed at a tertiary medical center, and the epidemiological features and risk factors of AKI found in the study population may therefore not be generalizable to patients in lower level hospitals.

The findings have important implications for research and patient care. We found an increasing incidence of CA-AKI among hospitalized adults and its risk profile underscored the need to increase awareness of AKI among policy makers and health professionals, to support the development of effective strategies for early identification and prevention of AKI. Further research into the longer-term outcomes of AKI is warranted.

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REFERENCES

1. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3365–3370.

2. Nolan CR, Anderson RJ. Hospital-acquired acute renal failure. *J Am Soc Nephrol.* 1998;9:710–718.

3. Zeng X, McMahon GM, Brunelli SM, et al. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol.* 2014;9:12–20.

4. Uchino S, Kellum JA, Bellomo R. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA.* 2005;294:813–818.

5. Mehta RL, Pascual MT, Soroko S. Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int.* 2004;66:1613–1621.

6. Kaufman J, Dhakal M, Patel B, et al. Community-acquired acute renal failure. *Am J Kidney Dis.* 1991;17:191–198.

7. Kaul A, Sharma RK, Tripathi R, et al. Spectrum of community-acquired acute kidney injury in India: a retrospective study. *Saudi J Kidney Dis Transpl.* 2012;23:619–628.

8. Schissler MM, Zaidi S, Kumar H, et al. Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. *Nephrology (Carlton).* 2013;18:183–187.

9. Prakash J, Singh TB, Ghosh B, et al. Changing epidemiology of community-acquired acute kidney injury in developing countries: analysis of 2405 cases in 26 years from eastern India. *Clin Kidney J.* 2013;6:150–155.

10. Der Mesropian PJ, Kalamaras JS, Eisele G, et al. Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. *Clin Nephrol.* 2014;81:174–184.

11. Sesso R, Roque A, Vicioso B, et al. Prognosis of ARF in hospitalized elderly patients. *Am J Kidney Dis.* 2004;44:410–419.

12. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet.* 2013;382:170–179.

13. Cerda J, Bagga A, Kher V, et al. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol.* 2008;4:138–153.

14. Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol.* 2007;18:1292–1298.

15. Dreischulte T, Morales DR, Bell S, et al. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin–angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int.* 2015;88:396–403.

16. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8:R204–R212.

17. Yokoyama H, Narita I, Sugiyama H, et al. Drug-induced kidney disease: a study of the Japan Renal Biopsy Registry from 2007 to 2015. *Clin Exp Nephrol.* 2015:1–11.

18. Cheng TM. Taiwan's new national health insurance program: genesis and experience so far. *Health Aff (Millwood).* 2003;22:61–76.

19. Lafrance JP, Miller DR. Defining acute kidney injury in database studies: the effects of varying the baseline kidney function assessment period and considering CKD status. *Am J Kidney Dis.* 2010;56:651–660.

20. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173:676–682.

21. Chao C-T, Tsai H-B, Wu C-Y, et al. Cumulative cardiovascular polypharmacy is associated with the risk of acute kidney injury in elderly patients. *Medicine.* 2015;94:e1251.

22. UK Medicines Inofmraiton. Guidelines for Medicines Optimisation in Patients with Acute Kidney Injury in Secondary Care. Retrieved from http://www.medicinesresources.nhs.uk/en/Medicines-Awareness/Other-Evidence/Implementation-support-tools/Guidelines-for-Medicines-Optimisation-in-Patients-with-Acute-Kidney-Injury-in-Secondary-Care/ [accessed April 30, 2016].

23. Chang CB, Yang SY, Lai HY, et al. Using published criteria to develop a list of potentially inappropriate medications for elderly patients in Taiwan. *Pharmacoepidemiol Drug Saf.* 2012;21:1269–1279.

24. Agresti A. Categorical Data Analysis. New York: John Wiley and Sons; 2002.

25. Wonnacott A, Meran S, Amphlett B, et al. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol.* 2014;9:1007–1014.

26. Hsu CY, Ordonez JD, Chertow GM, et al. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int.* 2008;74:101–107.

27. Koulouridis I, Price LL, Madias NE, et al. Hospital-acquired acute kidney injury and hospital readmission: a cohort study. *Am J Kidney Dis.* 2015;65:275–282.

28. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis.* 2002;39:930–936.

29. Shusterman N, Strom BL, Murray TG, et al. Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. *Am J Med.* 1987;83:65–71.

30. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA.* 2005;294:813–818.

31. Himmelfarb J, Ikizler TA. Acute kidney injury: changing lexicography, definitions, and epidemiology. *Kidney Int.* 2007;71:971–976.

32. Chao CT, Tsai HB, Wu CY, et al. Cumulative cardiovascular polypharmacy is associated with the risk of acute kidney injury in elderly patients. *Medicine (Baltimore).* 2015;94:e1251.

33. Waikar SS, Wald R, Chertow GM, et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J Am Soc Nephrol.* 2006;17:1688–1694.

34. Singer E, Elger A, Elitok S, et al. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int.* 2011;80:405–414.