

Impact of Acute Kidney Injury, Co-Existing with and without Chronic Kidney Disease on the Short-Term Adverse Outcomes Following Atherosclerotic Cardiovascular Disease Events in Patients with Diabetes

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Background/Objective: Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality among patients with diabetes mellitus (DM). Although ASCVD risk is elevated in diabetic populations, the effect of acute kidney injury (AKI), especially when chronic kidney disease (CKD) is present, on post-ASCVD outcomes remain unclear. This study investigates the association between AKI—with or without co-existing CKD—and short-term adverse outcomes in diabetic patients following their first ASCVD event.

Methods: This retrospective cohort study analyzed data from the Taipei Medical University Clinical Research Database (2004–2020), which includes anonymized electronic health records from three affiliated hospitals. Patients with DM who experienced the first ASCVD event were categorized by kidney function: no known kidney disease (NKD), AKI, CKD, and acute-on-CKD (AoCKD). The impact of kidney dysfunction on outcomes was assessed using Cox proportional-hazards models, with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Out of 4525 patients, those with CKD and AoCKD exhibited significantly higher 1-year all-cause mortality (HR: 1.24 and 1.68, respectively) and risks of cardiovascular death, recurrent ASCVD-related hospitalizations, and heart failure, compared with NKD patients. Diuretic use was associated with increased all-cause mortality in AoCKD and CKD groups. In the contrary, the use of metformin was associated with a lower risk of all-cause mortality in AoCKD and CKD groups.

Conclusion: AoCKD significantly increases short-term mortality and cardiovascular complications in diabetic patients post-ASCVD period, whereas AKI alone does not confer additional risk. These findings highlight the need for dedicated case-managed, personalized and multidisciplinary interventions for cardiorenal health. The early nephrologist consultation, echocardiography with speckle-tracking strain, urine albumin-to-creatinine ratio, pharmacologic strategies, such as cautious use of diuretics, use of sodium-glucose transport protein 2 inhibitors, statin or metformin are recommended to improve outcomes in this high-risk group.

Keywords: atherosclerotic cardiovascular disease, acute kidney injury, chronic kidney disease, cohort study, diabetes mellitus



Introduction

Diabetes mellitus (DM) is a global public health concern and is associated with high morbidity and mortality rates, particularly because of the heightened susceptibility of patients with DM to cardiovascular disease (CVD) relative to that of individuals without DM.¹ Atherosclerotic cardiovascular disease (ASCVD) is the principal cause of death and disability among patients with DM.^{1,2} The clinical manifestations of ASCVD in DM include coronary artery disease (CAD), ischemic stroke, and peripheral artery occlusive disease (PAOD).^{2,3} Predicting and reducing ASCVD events in patients with DM is clinically important.

Acute kidney injury (AKI) is characterized by a sudden decline in renal function, ranging from a minimal increase in serum creatinine levels to severe renal failure necessitating dialysis.^{4,5} AKI is a well-established risk factor for CKD, end-stage renal disease, and mortality.^{6,7} Furthermore, numerous studies have reported an association between AKI and CVD (acute coronary syndrome and congestive heart failure (CHF)).^{8–10} Studies also proved that AKI significantly increased long-term cardiovascular morbidity and mortality.^{11,12} However, these studies have primarily focused on specified populations at a high risk for ASCVD, and the impact of AKI on cardiovascular outcomes in diabetic patients following ASCVD events remains unclear.

Chronic kidney disease (CKD) is also prevalent among individuals with DM and is characterized by functional or structural abnormalities of the kidneys persisting for ≥ 3 months.¹³ The considerable impact of CKD on ASCVD risk has increasingly been recognized in the literature.¹⁴ Patients with both DM and CKD exhibit a disproportionately higher risk of ASCVD than do those with DM alone.^{15–17} CKD is recognized as an independent risk factor for CAD and cardiovascular complications following acute myocardial infarction (AMI).^{18,19} The presence of CKD has been identified as an independent risk factor for ASCVD. Recognizing CKD as a potent predictor of CVD, clinical guidelines now categorize patients with CKD as belonging to the highest risk group, emphasizing its importance in recommendations for the prevention, detection, and treatment of CVD.²⁰

Patients with DM are more susceptible to AKI with a high mortality rate and poor prognosis. Moreover, AKI occurs in approximately 25% of patients hospitalized with CVD.²¹ The impact of AKI, CKD or both on the post-ASCVD adverse outcomes in DM patients warrants further investigation. Therefore, in this study, we used the Taipei Medical University Clinical Research Database (TMUCRD) to explore the impact of AKI, with or without CKD, on short-term (1-year) adverse outcomes in diabetic patients following their first ASCVD event.

Methods

Data Source

The data used in this study were obtained from the TMUCRD,²² which contains the electronic health records of more than 4 million patients (spanning the years 1998 to 2021) from 3 affiliated teaching hospitals: Taipei Medical University Hospital, Wan Fang Hospital, and Shuang Ho Hospital. The patients' clinical data were collected between January 1, 2004, and December 31, 2020. All hospitals in Taiwan fall under the coverage of the National Health Insurance program, and the National Health Insurance Agency meticulously performs an expert review on a random sample of all medical records every quarter, and false diagnosis reports are given a severe penalty. This rigorous review process ensures the reliability and accuracy of the electronic health records used in this study for testing our hypothesis. This study was evaluated and approved by the Taipei Medical University-Institutional Review Board (TMU-JIRB-N202108073). The study was conducted in accordance with the local legislation and institutional requirements. The requirement for informed consent was waived by TMU-JIRB because all data were anonymized and de-identified before the analysis.

Study Population and Design

This study enrolled adult patients with DM, who had received a new clinical diagnosis of ASCVD, including CAD (*ICD-9-CM* codes 410–411; 413–414; *ICD-10-CM* codes I20–I25.1), stroke (*ICD-9-CM* codes 430–438; *ICD-10-CM* codes I60–I69), or PAOD (*ICD-9-CM* code 443.9; *ICD-10-CM* code I73.9). Patients undergoing dialysis, experiencing shock, or having an observation time of less than 1 month were excluded. The index date was defined as the date of ASCVD diagnosis. The AKI was defined as an abrupt deterioration of renal function within 7 days of the index date. We excluded

patients with a previous history of AKI within 1 year before the index day by using *ICD-9-CM* code 584 or *ICD-10-CM* code N17. The CKD was determined as an estimated glomerular filtration rate (eGFR) value of <60 mL/min/1.73 m² and urine protein dipstick value \geq trace on at least 2 occasions 90 days apart before the index date.²³ The entire cohort was stratified into 4 groups: no known kidney disease (NKD), AKI, CKD, and AKI and CKD (acute-on-CKD; AoCKD). Patients with AKI, CKD, and AoCKD were further matched to patients with NKD based on sex, age, index year, comorbidities, medications, and ASCVD diagnosis to form 3 distinct cohorts. Figure 1 presents a flowchart of the study process. Matching based on propensity score (PS) calculated through logistic regression was applied to establish the cohorts, with a matching ratio of 1:2 (one case to 2 controls).

Study Endpoint

The primary endpoints of this study were all-cause mortality; cardiovascular death; hospitalization due to CHF; and a range of ASCVD events, including stroke (hemorrhagic or ischemic), AMI, major adverse limb events (acute limb ischemia, major amputation, and need for surgical peripheral revascularization), and all cardiovascular events (cardiovascular death, CHF, and ASCVD). The cause of death was defined according to the discharge summaries recorded in the TMUCRD. Besides, TMUCRD has linked with the Ministry of Health and Welfare's death registration records, exhibiting accurate cause of death information for each deceased patient.²⁴ The follow-up period started from the index date until the occurrence of primary outcomes, loss of follow-up, 365 days after the index date, or until December 31, 2020, whichever came first.

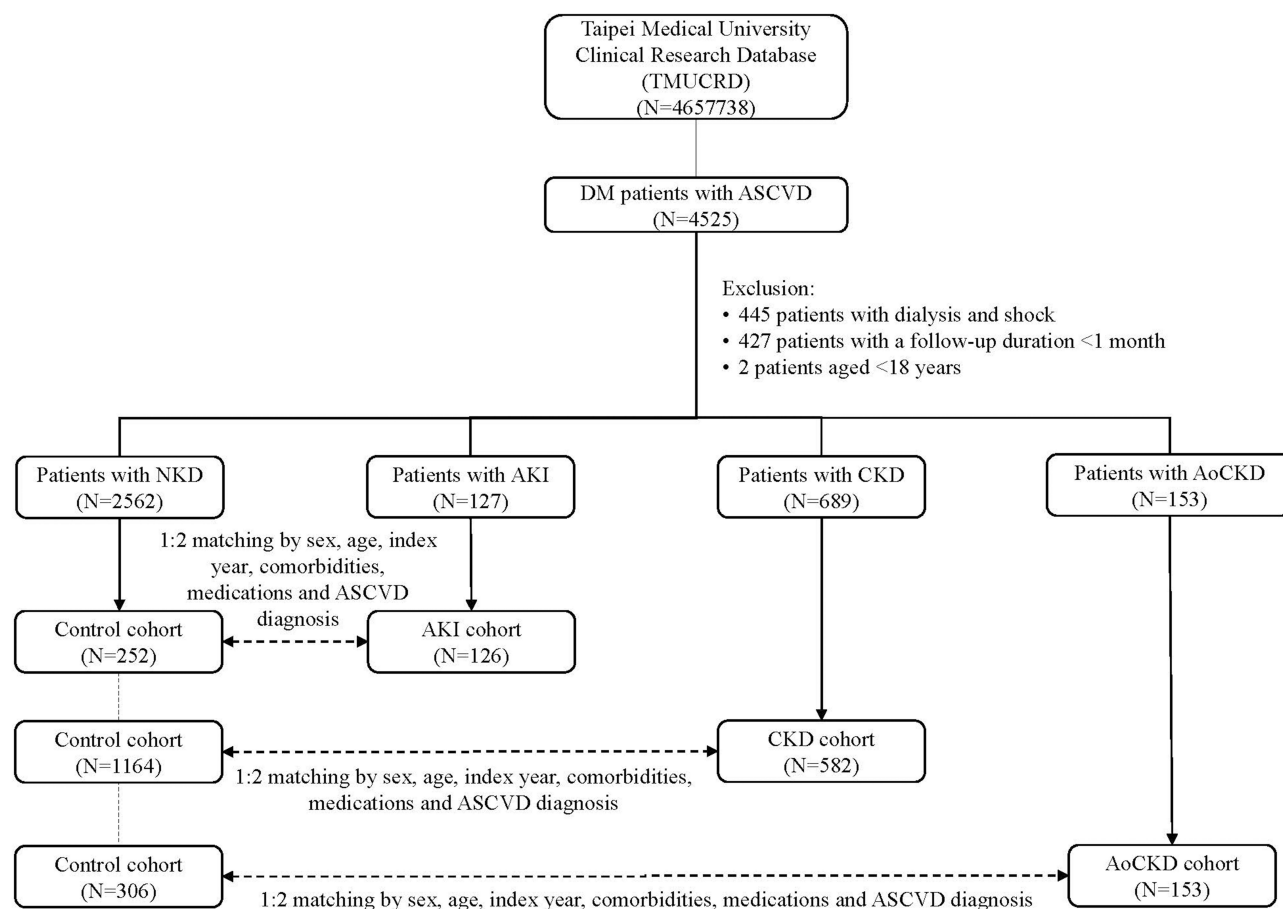


Figure 1 Flowchart of patient selection process.

Abbreviations: AKI, acute kidney injury; AoCKD, acute-on-chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; NKD, no known kidney disease.

Covariates

In addition to demographic variables, such as age, body mass index (BMI), and sex, some laboratory parameters, namely, left ventricular ejection fraction (LVEF), C-reactive protein (CRP) level, and glycated hemoglobin level, were collected for analysis. Comorbidities and medications for ASCVD and DM were also collected (Tables 1–3). Anatomical Therapeutic Chemical codes were used to identify medications, and drugs prescribed within the 2 years before the index date were considered. Comorbidities were defined based on 2 or more diagnostic records within the 2 years before the index date.

Table 1 Baseline Characteristics of Patients in AKI Cohort

| | Overall (n=378) | NKD (N=252) | AKI (N=126) | |
|--------------------------|-----------------|---------------|---------------|--------|
| Variable | Mean±SD/n (%) | Mean±SD/n (%) | Mean±SD/n (%) | P |
| Age (y) | 67.25±12.97 | 67.76±12.57 | 66.25±13.73 | 0.286 |
| BMI (kg/m ²) | 25.92±4.80 | 26.21±4.672 | 25.38±5.009 | 0.225 |
| Sex, n (%) | | | | 0.215 |
| Female | 176 (46.56%) | 123 (48.81%) | 53 (42.06%) | |
| Male | 202 (53.44%) | 129 (51.19%) | 73 (57.94%) | |
| Laboratory data | | | | |
| LVEF | 64.67±11.92 | 62.99±12.24 | 65.44±13.00 | 0.266 |
| CRP | 4.15±4.06 | 3.894±3.851 | 4.610±4.431 | 0.409 |
| HbA1c | 7.70±1.82 | 7.909±1.871 | 7.382±1.720 | 0.087 |
| Comorbidities, n (%) | | | | |
| HTN | 203 (53.70%) | 133 (52.78%) | 70 (55.56%) | 0.942 |
| HPL | 172 (45.50%) | 120 (47.62%) | 52 (41.27%) | 0.825 |
| Medication, n (%) | | | | |
| Diuretics | 166 (43.92%) | 108 (42.86%) | 58 (46.03%) | 0.771 |
| Antiplatelets | 355 (93.92%) | 238 (94.44%) | 117 (92.86%) | >0.999 |
| Warfarin | 24 (6.35%) | 15 (5.95%) | 9 (7.14%) | 0.596 |
| Rivaroxaban | 10 (2.65%) | 6 (2.38%) | 4 (3.17%) | 0.842 |
| ACEI/ARB | 272 (71.96%) | 184 (73.02%) | 88 (69.84%) | 0.936 |
| Beta-2 blockers | 276 (73.02%) | 184 (73.02%) | 92 (73.02%) | 0.677 |
| CCBs | 336 (88.89%) | 224 (88.89%) | 112 (88.89%) | 0.629 |
| Statin | 272 (71.96%) | 180 (71.43%) | 92 (73.02%) | 0.804 |
| Metformin | 208 (55.03%) | 138 (54.76%) | 70 (55.56%) | 0.610 |
| Thiazolidinedione | 35 (9.26%) | 22 (8.73%) | 13 (10.32%) | 0.807 |
| Sulfonylureas | 140 (37.04%) | 91 (36.11%) | 49 (38.89%) | 0.707 |
| AGIs | 67 (17.72%) | 43 (17.06%) | 24 (19.05%) | 0.316 |
| DPP4Is | 124 (32.80%) | 79 (31.35%) | 45 (35.71%) | 1.000 |
| Insulin | 16 (4.23%) | 10 (3.97%) | 6 (4.76%) | 0.761 |

(Continued)

Table 1 (Continued).

| | Overall (n=378) | NKD (N=252) | AKI (N=126) | |
|-------------------------------|-----------------|---------------|---------------|-------|
| Variable | Mean±SD/n (%) | Mean±SD/n (%) | Mean±SD/n (%) | P |
| ASCVD diagnosis, n (%) | | | | |
| CAD | 275 (72.75%) | 183 (72.62%) | 92 (73.02%) | 0.934 |
| Stroke | 57 (15.08%) | 37 (14.68%) | 20 (15.87%) | 0.760 |
| PAOD | 49 (12.96%) | 34 (13.49%) | 15 (11.90%) | 0.665 |

Notes: Continuous variables were assessed using the Student *t* test. Categorical variables were assessed using the chi-squared test.

Abbreviations: NKD, no known kidney disease; LVEF, left ventricular ejection fraction; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; HTN, hypertension; HPL, hyperlipidemia; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers; AGIs, Alpha-glucosidase inhibitors; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DPP4Is, Dipeptidyl peptidase-4 inhibitors; PAOD, peripheral arterial occlusion disease.

Statistical Analysis

The baseline characteristics of the patients are summarized as means and standard deviations for continuous variables and counts and percentages for categorical variables. Differences between 2 groups were assessed using the student *t* test for continuous variables and the chi-square test for categorical variables. Univariable and multivariable Cox proportional regression models were employed to estimate crude HRs and adjusted HRs (aHRs), with 95% confidence intervals (CIs). The aHR was derived after adjustment to all variables listed in Tables 1–3. The cumulative incidence rate was determined by using the Kaplan–Meier method, with error bars in the graph used to present HRs. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and graphs were generated using R version 4.1.0. The significance level was set at a *P* value of <0.05.

Table 2 Baseline Characteristics of Patients in CKD Cohort

| | Overall (n=1746) | NKD (N=1164) | CKD (N=582) | |
|-------------------------------|------------------|--------------|--------------|-------|
| Variable | Mean±SD | Mean±SD | Mean±SD | P |
| Age (y) | 69.43±11.75 | 69.37±11.72 | 69.55±11.81 | 0.760 |
| BMI (kg/m²) | 25.91±5.08 | 26.15±5.072 | 25.44±5.083 | 0.052 |
| Sex, n (%) | | | | 0.603 |
| Female | 687 (39.35%) | 463 (39.78%) | 224 (38.49%) | |
| Male | 1059 (60.65%) | 701 (60.22%) | 358 (61.51%) | |
| Laboratory data | | | | |
| LVEF | 63.59±12.42 | 63.52±12.20 | 63.71±12.81 | 0.856 |
| CRP | 4.42±4.45 | 4.474±4.616 | 4.336±4.191 | 0.727 |
| HbA1c | 7.60±1.79 | 7.691±1.889 | 7.432±1.596 | 0.065 |
| Comorbidities, n (%) | | | | |
| HTN | 989 (56.64%) | 655 (56.27%) | 334 (57.39%) | 0.657 |
| HPL | 594 (34.02%) | 402 (34.54%) | 192 (32.99%) | 0.520 |

(Continued)

Table 2 (Continued).

| | Overall (n=1746) | NKD (N=1164) | CKD (N=582) | |
|-------------------------------|------------------|---------------|--------------|-------|
| Variable | Mean±SD | Mean±SD | Mean±SD | P |
| Medication, n (%) | | | | |
| Diuretics | 888 (50.86%) | 590 (50.69%) | 298 (51.20%) | 0.839 |
| Antiplatelets | 1627 (93.18%) | 1086 (93.30%) | 541 (92.96%) | 0.788 |
| Warfarin | 166 (9.51%) | 109 (9.36%) | 57 (9.79%) | 0.773 |
| Rivaroxaban | 84 (4.81%) | 58 (4.98%) | 26 (4.47%) | 0.635 |
| ACEI/ARB | 1228 (70.33%) | 825 (70.88%) | 403 (69.24%) | 0.482 |
| Beta-2 blockers | 1221 (69.93%) | 815 (70.02%) | 406 (69.76%) | 0.912 |
| CCBs | 1305 (74.74%) | 868 (74.57%) | 437 (75.09%) | 0.815 |
| Statin | 1113 (63.75%) | 745 (64.00%) | 368 (63.23%) | 0.751 |
| Metformin | 913 (52.29%) | 613 (52.66%) | 300 (51.55%) | 0.660 |
| Thiazolidinedione | 152 (8.71%) | 105 (9.02%) | 47 (8.08%) | 0.509 |
| Sulfonylureas | 717 (41.07%) | 477 (40.98%) | 240 (41.24%) | 0.918 |
| AGIs | 292 (16.72%) | 192 (16.49%) | 100 (17.18%) | 0.717 |
| DPP4Is | 620 (35.51%) | 408 (35.05%) | 212 (36.43%) | 0.572 |
| Insulin | 68 (3.89%) | 46 (3.95%) | 22 (3.78%) | 0.861 |
| ASCVD diagnosis, n (%) | | | | |
| CAD | 815 (46.68%) | 546 (46.91%) | 269 (46.22%) | 0.786 |
| Stroke | 577 (33.05%) | 387 (33.25%) | 190 (32.65%) | 0.801 |
| PAOD | 363 (20.79%) | 237 (20.36%) | 126 (21.65%) | 0.532 |

Notes: Continuous variables were assessed using the Student *t* test. Categorical variables were assessed using the chi-squared test.

Abbreviations: NKD, no known kidney disease; LVEF, left ventricular ejection fraction; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; HTN, hypertension; HPL, hyperlipidemia; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers; AGIs, Alpha-glucosidase inhibitors; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DPP4Is, Dipeptidyl peptidase-4 inhibitors; PAOD, peripheral arterial occlusion disease.

Table 3 Baseline Characteristics of Patients in AoCKD Cohort

| | Overall (n=459) | NKD (N=306) | AoCKD (N=153) | |
|-------------------------------|-----------------|--------------|---------------|-------|
| Variable | Mean±SD | Mean±SD | Mean±SD | P |
| Age (y) | 69.36±12.75 | 69.31±12.71 | 69.46±12.86 | 0.905 |
| BMI (kg/m²) | 25.91±4.68 | 25.58±4.936 | 26.47±4.189 | 0.155 |
| Sex, n (%) | | | | 0.894 |
| Female | 197 (42.92%) | 132 (43.14%) | 65 (42.48%) | |
| Male | 262 (57.08%) | 174 (56.86%) | 88 (57.52%) | |

(Continued)

Table 3 (Continued).

| | Overall (n=459) | NKD (N=306) | AoCKD (N=153) | |
|-------------------------------|-----------------|--------------|---------------|-------|
| Variable | Mean±SD | Mean±SD | Mean±SD | P |
| Laboratory data | | | | |
| LVEF | 63.40±12.72 | 62.78±13.02 | 64.30±12.31 | 0.434 |
| CRP | 5.06±4.44 | 4.515±4.345 | 5.842±4.499 | 0.057 |
| HbA1c | 7.57±1.82 | 7.601±1.842 | 7.509±1.794 | 0.731 |
| Comorbidities, n (%) | | | | |
| HTN | 257 (55.99%) | 167 (54.58%) | 90 (58.82%) | 0.387 |
| HPL | 163 (35.51%) | 107 (34.97%) | 56 (36.60%) | 0.730 |
| Medication, n (%) | | | | |
| Diuretics | 304 (66.23%) | 197 (64.38%) | 107 (69.93%) | 0.235 |
| Antiplatelets | 449 (97.82%) | 301 (98.37%) | 148 (96.73%) | 0.258 |
| Warfarin | 36 (7.84%) | 22 (7.19%) | 14 (9.15%) | 0.461 |
| Rivaroxaban | 6 (1.31%) | 3 (0.98%) | 3 (1.96%) | 0.383 |
| ACEI/ARB | 344 (74.95%) | 229 (74.84%) | 115 (75.16%) | 0.939 |
| Beta-2 blockers | 347 (75.60%) | 230 (75.16%) | 117 (76.47%) | 0.759 |
| CCBs | 393 (85.62%) | 265 (86.60%) | 128 (83.66%) | 0.397 |
| Statin | 325 (70.81%) | 222 (72.55%) | 103 (67.32%) | 0.245 |
| Metformin | 229 (49.89%) | 155 (50.65%) | 74 (48.37%) | 0.644 |
| Thiazolidinedione | 25 (5.45%) | 18 (5.88%) | 7 (4.58%) | 0.561 |
| Sulfonylureas | 195 (42.48%) | 135 (44.12%) | 60 (39.22%) | 0.317 |
| AGIs | 92 (20.04%) | 64 (20.92%) | 28 (18.30%) | 0.510 |
| DPP4Is | 236 (51.42%) | 161 (52.61%) | 75 (49.02%) | 0.468 |
| Insulin | 29 (6.32%) | 18 (5.88%) | 11 (7.19%) | 0.587 |
| ASCVD diagnosis, n (%) | | | | |
| CAD | 312 (67.97%) | 213 (69.61%) | 99 (64.71%) | 0.289 |
| Stroke | 74 (16.12%) | 47 (15.36%) | 27 (17.65%) | 0.530 |
| PAOD | 82 (17.86%) | 53 (17.32%) | 29 (18.95%) | 0.667 |

Notes: Continuous variables were assessed using the Student t test. Categorical variables were assessed using the chi-squared test.

Abbreviations NKD, no known kidney disease; AoCKD, acute-on-CKD; LVEF, left ventricular ejection fraction; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HTN, hypertension; HPL, hyperlipidemia; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers; AGIs, Alpha-glucosidase inhibitors; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DPP4Is, Dipeptidyl peptidase-4 inhibitors; PAOD, peripheral arterial occlusion disease.

Results

From the 4,657,738 patients with records in the TMUCRD, we identified 4525 with ASCVD between 2008 and 2019. Among them, 2562, 127, 689, and 153 patients were attributed to the NKD, AKI, CKD, and AoCKD, respectively. Subsequently, the

AKI, CKD, and AoCKD cohorts were matched with the NKD cohort (Figure 1). The baseline characteristics of the patients before the PS matching are presented (S1 Table). As presented in Table 1, the characteristics of the patients with AKI and NKD were similar, with an average age of 67.25 years, a mean BMI of 25.92, and 53.44% male representation. CAD (72.75%) was the predominant ASCVD diagnosis in this cohort. In Table 2, the baseline characteristics in the CKD comparison cohort exhibited no significant differences; the mean age and BMI were 69.43 years and 25.91, respectively, and approximately 60.65% of the patients were male. Regarding ASCVD diagnoses, 46.68% of the cases were CAD, 33.05% were stroke, and 20.79% were PAOD. No differences were noted in the baseline characteristics in the AoCKD comparison cohort (Table 3). The mean age and BMI in the AoCKD cohort were 69.36 years and 25.91, respectively, with a male predominance of 57.08%. The primary type of ASCVD in this cohort was CAD (67.97%).

Table 4 presents the risk associated with various CVD outcomes attributable to the 3 cohorts. Compared with the patients with NKD, those with CKD demonstrated a 1.66-fold increase in the risk of all CVD events (95% CI: 1.29–2.14), whereas the patients with AoCKD exhibited a 2.06-fold increase in the risk of all CVD events (95% CI: 1.29–3.27). The patients with CKD exhibited a significantly higher risk of hospitalization due to ASCVD (aHR=1.79; 95% CI=1.26–2.55), ACS (aHR=1.71; 95% CI=1.12–2.61), and cardiovascular death (aHR=1.70; 95% CI=1.12–2.57). The aHRs of hospitalization due to ACS, CHF, and cardiovascular death in the patients with AoCKD compared with those with NKD were 2.22 (95% CI=1.09–4.53), 3.40 (95% CI=1.55–7.47), and 3.02 (95% CI=1.37–6.63), respectively.

Table 4 Association Between AKI, CKD and AoCKD and CV Outcomes

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|-----------------------------------|-----|-----|------|------|-----------------|--------|------|-----------------|--------|
| All CV events | | | | | | | | | |
| AKI | 19 | 109 | 1.75 | 1.20 | (0.68, 2.11) | 0.524 | 1.36 | (0.76, 2.44) | 0.300 |
| CKD | 106 | 473 | 2.24 | 1.65 | (1.28, 2.12)*** | <0.001 | 1.66 | (1.29, 2.14)*** | <0.001 |
| AoCKD | 34 | 112 | 3.05 | 2.00 | (1.27, 3.16)** | 0.003 | 2.06 | (1.29, 3.27)** | 0.002 |
| Hospitalization for ASCVD | | | | | | | | | |
| AKI | 10 | 103 | 0.97 | 1.29 | (0.59, 2.84) | 0.527 | 1.30 | (0.56, 3.02) | 0.540 |
| CKD | 57 | 445 | 1.28 | 1.81 | (1.27, 2.57)*** | <0.001 | 1.79 | (1.26, 2.55)** | 0.001 |
| AoCKD | 15 | 105 | 1.43 | 1.72 | (0.89, 3.34) | 0.109 | 1.75 | (0.88, 3.46) | 0.110 |
| Hospitalization for ACS | | | | | | | | | |
| AKI | 8 | 107 | 0.75 | 1.19 | (0.50, 2.83) | 0.700 | 1.20 | (0.48, 3.00) | 0.695 |
| CKD | 39 | 463 | 0.84 | 1.79 | (1.17, 2.73)** | 0.007 | 1.71 | (1.12, 2.61)* | 0.013 |
| AoCKD | 15 | 108 | 1.38 | 2.01 | (1.01, 3.99)* | 0.046 | 2.22 | (1.09, 4.53)* | 0.028 |
| Hospitalization for stroke | | | | | | | | | |
| AKI | 2 | 104 | 0.19 | 2.08 | (0.29, 14.76) | 0.464 | 5.91 | (0.26, 133.07) | 0.264 |
| CKD | 18 | 459 | 0.39 | 1.97 | (1.04, 3.73)* | 0.036 | 2.08 | (1.09, 3.94)* | 0.025 |
| AoCKD | 0 | 104 | 0.00 | | | | | | |
| Hospitalization for PAOD | | | | | | | | | |
| AKI | 0 | 102 | 0.00 | NA | | | NA | | |
| CKD | 2 | 453 | 0.04 | 0.56 | (0.12, 2.63) | 0.462 | 0.56 | (0.12, 2.68) | 0.471 |
| AoCKD | 0 | 104 | 0.00 | NA | | | NA | | |

(Continued)

Table 4 (Continued).

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|--------------------------------|-----|-----|------|------|----------------|--------|------|-----------------|--------|
| Hospitalization for CHF | | | | | | | | | |
| AKI | 7 | 103 | 0.68 | 1.61 | (0.60, 4.31) | 0.348 | 1.50 | (0.49, 4.56) | 0.473 |
| CKD | 22 | 440 | 0.50 | 1.22 | (0.73, 2.05) | 0.446 | 1.27 | (0.76, 2.15) | 0.362 |
| AoCKD | 15 | 105 | 1.42 | 3.08 | (1.44, 6.59)** | 0.004 | 3.40 | (1.55, 7.47)** | 0.002 |
| Cardiovascular death | | | | | | | | | |
| AKI | 5 | 107 | 0.47 | 0.80 | (0.29, 2.25) | 0.676 | 0.94 | (0.29, 3.00) | 0.917 |
| CKD | 40 | 460 | 0.87 | 1.69 | (1.12, 2.55)* | 0.012 | 1.70 | (1.12, 2.57)* | 0.012 |
| AoCKD | 14 | 108 | 1.30 | 2.61 | (1.23, 5.57)* | 0.013 | 3.02 | (1.37, 6.63)** | 0.006 |
| All-cause mortality | | | | | | | | | |
| AKI | 38 | 109 | 3.49 | 0.93 | (0.63, 1.36) | 0.699 | 0.93 | (0.62, 1.37) | 0.699 |
| CKD | 265 | 473 | 5.60 | 1.25 | (1.07, 1.45)** | 0.004 | 1.24 | (1.06, 1.44)** | 0.006 |
| AoCKD | 79 | 112 | 7.08 | 1.58 | (1.19, 2.09)** | 0.0014 | 1.68 | (1.26, 2.25)*** | <0.001 |

Notes: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Abbreviations: NKD, no known kidney disease; AoCKD, acute-on-CKD; N, number of events; PY, person-years; IR, incidence rate (per 10 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; PAOD, peripheral arterial occlusion disease; CHF, congestive heart failure.

Both the patients with CKD (aHR=1.24; 95% CI=1.06–1.44) and AoCKD (aHR=1.68; 95% CI=1.26–2.25) demonstrated an increased likelihood of experiencing all-cause mortality compared with the patients with NKD.

In the AoCKD cohort, our findings revealed the diuretics users were associated with an increased risk of all-cause mortality, whereas metformin users were associated with a reduced risk of all-cause mortality (Table 5). In the AKI cohort (S2 Table), our findings revealed the associations between diuretics, alpha-glucosidase inhibitors, insulin and all CV events. For hospitalization due to ASCVD, users of insulin had a higher risk than nonusers did. The use of

Table 5 Association Between Medication and CV Outcomes in AoCKD Cohort

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|----------------------|----|-----|------|------|---------------|-------|------|--------------|-------|
| All CV events | | | | | | | | | |
| Medication | | | | | | | | | |
| Diuretics | 57 | 248 | 2.30 | 1.75 | (1.03, 2.97)* | 0.039 | 1.62 | (0.92, 2.86) | 0.097 |
| Statin | 56 | 276 | 2.03 | 1.16 | (0.69, 1.95) | 0.576 | 1.30 | (0.73, 2.33) | 0.373 |
| Metformin | 31 | 203 | 1.53 | 0.63 | (0.40, 0.99)* | 0.048 | 0.73 | (0.42, 1.27) | 0.263 |
| Thiazolidinedione | 4 | 23 | 1.77 | 0.91 | (0.33, 2.48) | 0.848 | 1.14 | (0.40, 3.28) | 0.802 |
| Sulfonylureas | 28 | 174 | 1.61 | 0.72 | (0.45, 1.15) | 0.164 | 0.74 | (0.41, 1.32) | 0.311 |
| AGIs | 19 | 79 | 2.40 | 1.32 | (0.78, 2.22) | 0.297 | 1.41 | (0.78, 2.54) | 0.254 |
| DPP4Is | 37 | 200 | 1.85 | 0.89 | (0.57, 1.41) | 0.627 | 0.99 | (0.59, 1.66) | 0.962 |
| Insulin | 5 | 23 | 2.15 | 1.09 | (0.44, 2.71) | 0.846 | 0.76 | (0.29, 1.99) | 0.583 |

(Continued)

Table 5 (Continued).

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|----------------------------------|-----|-----|-------|------|-----------------|--------|------|-----------------|--------|
| Hospitalization for ASCVD | | | | | | | | | |
| Medication | | | | | | | | | |
| Diuretics | 21 | 229 | 0.92 | 0.82 | (0.42, 1.59) | 0.560 | 0.84 | (0.40, 1.75) | 0.640 |
| Statin | 28 | 260 | 1.08 | 1.39 | (0.63, 3.05) | 0.409 | 1.63 | (0.66, 4.00) | 0.288 |
| Metformin | 15 | 193 | 0.78 | 0.64 | (0.33, 1.24) | 0.182 | 0.63 | (0.28, 1.41) | 0.260 |
| Thiazolidinedione | 3 | 22 | 1.39 | 1.45 | (0.45, 4.73) | 0.537 | 1.73 | (0.48, 6.21) | 0.399 |
| Sulfonylureas | 13 | 165 | 0.79 | 0.69 | (0.35, 1.36) | 0.281 | 0.56 | (0.24, 1.30) | 0.175 |
| AGIs | 11 | 74 | 1.49 | 1.73 | (0.85, 3.51) | 0.130 | 2.10 | (0.91, 4.84) | 0.082 |
| DPP4Is | 19 | 192 | 0.99 | 1.01 | (0.53, 1.95) | 0.972 | 1.07 | (0.48, 2.35) | 0.873 |
| Insulin | 2 | 21 | 0.96 | 0.95 | (0.23, 3.96) | 0.944 | 0.97 | (0.21, 4.37) | 0.964 |
| Cardiovascular death | | | | | | | | | |
| Medication | | | | | | | | | |
| Diuretics | 25 | 238 | 1.05 | 7.05 | (1.67, 29.77)** | 0.008 | 6.05 | (1.35, 27.07)* | 0.019 |
| Statin | 19 | 266 | 0.71 | 0.93 | (0.41, 2.13) | 0.869 | 1.21 | (0.47, 3.10) | 0.699 |
| Metformin | 10 | 199 | 0.50 | 0.50 | (0.23, 1.10) | 0.086 | 0.86 | (0.35, 2.12) | 0.742 |
| Thiazolidinedione | 2 | 22 | 0.90 | 1.27 | (0.30, 5.35) | 0.747 | 2.55 | (0.53, 12.18) | 0.241 |
| Sulfonylureas | 7 | 169 | 0.41 | 0.42 | (0.18, 0.99)* | 0.047 | 0.39 | (0.14, 1.12) | 0.081 |
| AGIs | 7 | 76 | 0.92 | 1.37 | (0.58, 3.23) | 0.477 | 1.54 | (0.58, 4.09) | 0.389 |
| DPP4Is | 12 | 197 | 0.61 | 0.71 | (0.33, 1.51) | 0.371 | 0.75 | (0.31, 1.80) | 0.522 |
| Insulin | 2 | 22 | 0.89 | 1.25 | (0.30, 5.26) | 0.765 | 0.64 | (0.14, 2.96) | 0.571 |
| All-cause mortality | | | | | | | | | |
| Medication | | | | | | | | | |
| Diuretics | 175 | 248 | 7.06 | 3.02 | (2.08, 4.38)*** | <0.001 | 2.10 | (1.42, 3.12)*** | <0.001 |
| Statin | 126 | 276 | 4.57 | 0.59 | (0.45, 0.78)*** | <0.001 | 0.82 | (0.59, 1.13) | 0.221 |
| Metformin | 68 | 203 | 3.35 | 0.41 | (0.30, 0.54)*** | <0.001 | 0.60 | (0.43, 0.85)** | 0.004 |
| Thiazolidinedione | 6 | 23 | 2.66 | 0.46 | (0.20, 1.03) | 0.060 | 0.77 | (0.33, 1.78) | 0.538 |
| Sulfonylureas | 67 | 174 | 3.84 | 0.54 | (0.40, 0.72)*** | <0.001 | 0.74 | (0.51, 1.05) | 0.095 |
| AGIs | 49 | 79 | 6.19 | 1.18 | (0.85, 1.62) | 0.318 | 1.26 | (0.88, 1.81) | 0.212 |
| DPP4Is | 98 | 200 | 4.89 | 0.78 | (0.60, 1.03) | 0.077 | 1.06 | (0.78, 1.46) | 0.697 |
| Insulin | 25 | 23 | 10.75 | 2.12 | (1.40, 3.22)*** | <0.001 | 1.41 | (0.90, 2.21) | 0.136 |

Notes: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Abbreviations: N, number of events; PY, person-years; IR, incidence rate (per 10 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; AGIs, Alpha-glucosidase inhibitors; ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; DPP4Is, Dipeptidyl peptidase-4 inhibitors; PAOD, peripheral arterial occlusion disease; CHF, congestive heart failure.

sulfonylureas and insulin were associated with the risk of cardiovascular death, and the use of diuretics and insulin were associated with the risk of all-cause mortality. The [S3 Table](#) presents the adverse outcomes in the CKD cohort. The use of diuretics was associated with all CV events. The use of diuretics or insulin was associated with an increased risk of all-cause mortality, whereas the use of statin, and metformin was associated with a lower risk of all-cause mortality. The data in [S4 Table](#) provide insights into the association between AKI, CKD, and AoCKD and CV events in diuretics users.

As indicated in [Table 6](#), each unit increase in CRP increased the risk of cardiovascular death by 1.58 times (95% CI=1.10–2.27). Notably, BMI was a protective factor for all-cause mortality in the AoCKD cohort. As indicated in [S5 Table](#),

Table 6 Association Between Baseline Variables and CV Outcomes in AoCKD Cohort

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|-----------------------------|----|-----|------|------|----------------|-------|------|---------------|-------|
| All CV events | | | | | | | | | |
| Age (y) | | | | 1.10 | (0.92, 1.30) | 0.303 | 0.98 | (0.49, 1.97) | 0.96 |
| BMI (kg/m ²) | | | | 0.84 | (0.58, 1.21) | 0.343 | 0.79 | (0.32, 1.99) | 0.618 |
| Sex, n (%) | | | | | | | | | |
| Female | 26 | 166 | 1.57 | 1.00 | (reference) | – | 1.00 | (reference) | – |
| Male | 49 | 220 | 2.23 | 1.43 | (0.89, 2.29) | 0.144 | 3.04 | (0.55, 16.96) | 0.205 |
| Laboratory data | | | | | | | | | |
| LVEF | | | | 0.85 | (0.63, 1.14) | 0.280 | 0.73 | (0.44, 1.21) | 0.226 |
| CRP | | | | 1.20 | (1.04, 1.37)* | 0.011 | 0.88 | (0.46, 1.70) | 0.710 |
| HbA1c | | | | 0.91 | (0.64, 1.29) | 0.585 | 0.82 | (0.31, 2.17) | 0.685 |
| Comorbidities, n (%) | | | | | | | | | |
| HTN | 46 | 217 | 2.12 | 1.23 | (0.77, 1.96) | 0.378 | 4.15 | (0.66, 26.07) | 0.129 |
| HPL | 25 | 135 | 1.85 | 0.92 | (0.57, 1.48) | 0.728 | 0.29 | (0.03, 2.91) | 0.294 |
| Cardiovascular death | | | | | | | | | |
| Age (y) | | | | 1.36 | (1.00, 1.85)* | 0.049 | 1.21 | (0.72, 2.05) | 0.469 |
| BMI (kg/m ²) | | | | 0.68 | (0.35, 1.32) | 0.253 | 0.72 | (0.34, 1.49) | 0.371 |
| Sex, n (%) | | | | | | | | | |
| Female | 13 | 166 | 0.78 | 1.00 | (reference) | – | 1.00 | (reference) | – |
| Male | 14 | 220 | 0.64 | 0.83 | (0.39, 1.76) | 0.627 | 0.84 | (0.23, 3.12) | 0.794 |
| Laboratory data | | | | | | | | | |
| LVEF | | | | 0.67 | (0.37, 1.23) | 0.195 | 0.35 | (0.05, 2.50) | 0.295 |
| CRP | | | | 1.28 | (1.08, 1.52)** | 0.004 | 1.58 | (1.10, 2.27)* | 0.014 |
| HbA1c | | | | 0.98 | (0.57, 1.69) | 0.942 | 0.98 | (0.49, 1.96) | 0.950 |
| Comorbidities, n (%) | | | | | | | | | |
| HTN | 17 | 217 | 0.78 | 1.34 | (0.61, 2.93) | 0.462 | 0.57 | (0.13, 2.50) | 0.456 |
| HPL | 11 | 135 | 0.82 | 1.24 | (0.57, 2.66) | 0.590 | 1.43 | (0.32, 6.45) | 0.641 |

(Continued)

Table 6 (Continued).

| | N | PY | IR | cHR | (95% CI) | P | aHR | (95% CI) | P |
|--------------------------|-----|-----|------|------|-----------------|--------|------|---------------|--------|
| All-cause mortality | | | | | | | | | |
| Age (y) | | | | 1.55 | (1.38, 1.74)*** | <0.001 | 1.50 | (1.08, 2.09)* | 0.0154 |
| BMI (kg/m ²) | | | | 0.60 | (0.48, 0.76)*** | <0.001 | 0.50 | (0.27, 0.91)* | 0.024 |
| Sex, n (%) | | | | | | | | | |
| Female | 100 | 166 | 6.04 | 1.00 | (reference) | - | 1.00 | (reference) | - |
| Male | 108 | 220 | 4.91 | 0.82 | (0.62, 1.07) | 0.141 | 1.56 | (0.57, 4.30) | 0.386 |
| Laboratory data | | | | | | | | | |
| LVEF | | | | 0.88 | (0.73, 1.06) | 0.186 | 0.88 | (0.64, 1.22) | 0.449 |
| CRP | | | | 1.22 | (1.13, 1.31)*** | <0.001 | 1.08 | (0.81, 1.42) | 0.613 |
| HbA1c | | | | 0.90 | (0.72, 1.12) | 0.337 | 0.89 | (0.61, 1.30) | 0.543 |
| Comorbidities, n (%) | | | | | | | | | |
| HTN | 144 | 217 | 6.65 | 0.94 | (0.71, 1.23) | 0.650 | 0.82 | (0.31, 2.19) | 0.696 |
| HPL | 68 | 135 | 5.04 | 0.89 | (0.67, 1.19) | 0.425 | 1.17 | (0.51, 2.67) | 0.708 |

Notes: **P*<0.05; ***P*<0.01; ****P*<0.001.
Abbreviations: N, number of events; PY, person-years; IR, incidence rate (per 10 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; CV, cardiovascular; BMI, body mass index; LVEF, left ventricular ejection fraction; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HTN, hypertension; HPL, hyperlipidemia.

in the AKI cohort, the higher the LVEF was, the lower were the risks of CV events and all-cause mortality. In the CKD cohort, BMI was negatively associated with cardiovascular death and all-cause mortality ([S6 Table](#)).

[Figure 2](#) presents the HRs for different outcomes across the 3 cohorts over 1-year interval. [Figure 3](#) illustrates the cumulative incidence of all cardiovascular events, hospitalization due to ASCVD, CHF, cardiovascular mortality, and all-cause mortality in the 3 cohorts.

Discussion

Our retrospective cohort study revealed 3 major findings. First, patients with AoCKD or CKD have significantly higher risks of all-cause mortality, cardiovascular death, and all cardiovascular events than do those with NKD. Second, the AoCKD group exhibited higher risks of all-cause mortality, cardiovascular death, and all cardiovascular events than the CKD group did, highlighting the compounding effect of AKI on pre-existing CKD. In contrast, patients with AKI alone had the same level of risk as compared to those with NKD, suggesting that AKI without underlying CKD may not independently increase cardiovascular risk. Third, diuretics use was associated with increased all-cause mortality risks in patients with AoCKD and among them, advanced age and lower BMI were independent predictors of all-cause mortality. Our findings provide critical evidence supporting the influence of AoCKD on the post-ASCVD outcomes in patients with DM. While prior studies have demonstrated an association between CKD and cardiovascular complications, our results emphasize that the coexistence of AKI and CKD represents a distinct and more severe risk profile, which needs critical clinical attention.

Our findings indicate that AKI might pose an additional risk either when it coexists with CKD at admission or progresses to CKD during follow-up. A systematic review and meta-analysis of 25 cohort studies highlighted the independent association of AKI with an increased risk of cardiovascular mortality, CHF, and AMI.¹¹ However, CKD status was not addressed in approximately one-third of the included studies. Our data helps to fill this knowledge gap. A clinical study involving 1371 participants demonstrated a strong correlation between AKI and all-cause mortality in

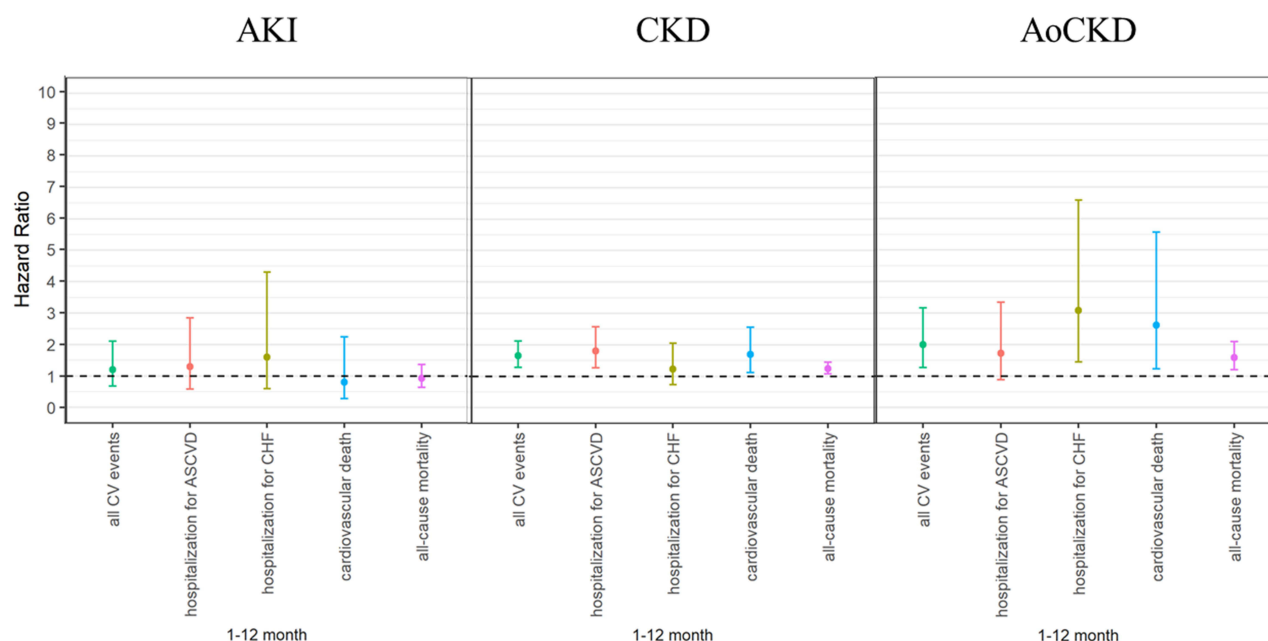


Figure 2 Adjusted hazard ratios for all cardiovascular events, hospitalization due to ASCVD or CHF events, cardiovascular death, and all-cause mortality, with 95% confidence intervals for the AKI cohort, CKD cohort, and AoCKD cohort across 1 year interval.

Abbreviations: AKI, acute kidney injury; AoCKD, acute-on-chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular.

patients with AMI.²⁵ The presence of admission $eGFR < 60 \text{ mL/min/1.73 m}^2$ in patients with AKI was associated with an increased risk of mortality, which is consistent with our study findings. Another analysis focusing on the impact of AKI on CHF found that AKI and its progression to CKD or severe AKI are linked to a poorer prognosis.²⁶ In addition, a study reported that patients who developed AKI after a stroke had a higher mortality risk, with an odds ratio of 2.45, than that of those without AKI, highlighting the impact of renal dysfunction in clinical outcomes.²⁷ However, the study had limitations, including a predominantly US-based patient population (99.9%), which may limit generalizability, potential ascertainment bias from focusing on high-income countries, and high heterogeneity in the meta-analysis. Cohort studies investigating the impact of AKI occurrence in patients with PAOD are scarce.^{28,29} Nevertheless, such studies have indicated that AKI is associated with in-hospital and 2-years mortality.^{28,29} In the present study, the stroke and PAOD populations were relatively small and underpowered to detect significant differences. Further large multicenter studies can be conducted to provide more conclusive evidence. Our patients with AKI alone did not elevate the post-ASCVD short-term risks. The plausible explanation includes transient systemic effects and less severe underlying illness in this group of patients. Besides, the LVEF is negatively associated with adverse effects in AKI cohort, which possibly imply the predicted poor prognosis of AKI due to systolic heart failure. On the other hands, among patients with AMI, larger infarction area, the use of iodinated radiocontrast material during coronary interventional and higher Killip classification is associated with a higher risk of AKI. Whether this association is causal or reflection underlying comorbid conditions remain unknown.

AKI may contribute to the development and progression of CKD, with the transition from AKI to CKD carrying an unfavorable prognosis. AKI itself has proved an increased risk of CKD, especially in patients with DM.^{6,7,30} Our data reveal a higher risk of CVD events in patients with DM with AoCKD than those with CKD alone. The pathophysiological mechanisms underlying AoCKD potentially involve activation of several signaling pathways (TGF- β , p53, and hypoxia-inducible factor), mitochondrial dysfunction, renal interstitial fibrosis, excess oxidative stress, aberrant autophagy, chronic inflammation, and endothelial dysfunction.^{31–35} Such pathological changes alterations may contribute to heightened injury and suppressed repair mechanisms and result in poor ASCVD outcomes in patients with AoCKD versus CKD alone. Targeting specific factors (cytokines, autophagy, and mitochondrial function) to prevent the AKI-to-

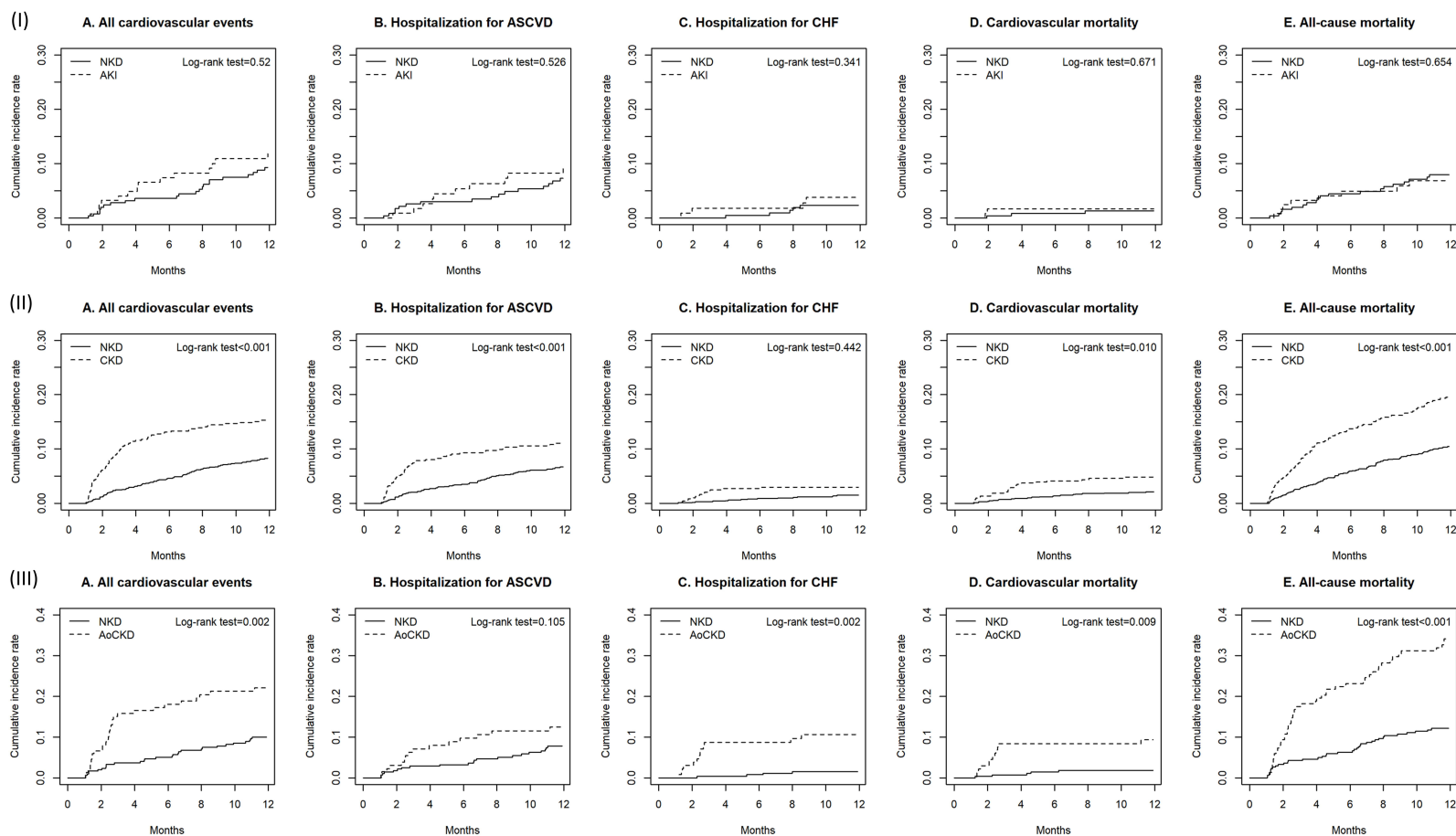


Figure 3 Kaplan–Meier curves depicting the cumulative incidence of **(A)** all cardiovascular events, **(B)** hospitalization due to ASCVD, **(C)** hospitalization due to CHF, **(D)** cardiovascular mortality, and **(E)** all-cause mortality in the **(I)** AKI cohort, **(II)** CKD cohort, and **(III)** AoCKD cohort.

Abbreviations: AKI, acute kidney injury; AoCKD, acute-on-chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; NKD, no known kidney disease.

CKD transition has potential to enhance cardiovascular outcomes and reduce mortality.^{32,34,35} Furthermore, albuminuria, represented by the urine albumin-to-creatinine ratio (uACR), is a robust marker of kidney damage in patients with DM.³⁶ The uACR in AKI or CKD may serve as a crucial nontraditional novel biomarker for predicting major ASCVD events.^{36–39} In a matched cohort study involving 1538 participants, a higher post-AKI uACR was discovered to be associated with an increased risk of CKD progression, highlighting the potential role of post-AKI uACR as a cardiorenal risk discriminator.⁴⁰ Given these pathophysiological mechanisms, patients with AoCKD require close monitoring and proactive interventions to mitigate cardiovascular complications.

In the subgroup analysis, we observed advanced age and lower BMI were associated with all-cause mortality in patients with CKD or AoCKD. The result of BMI was consistent with “obesity paradox” found in CKD cohort studies.^{41–43} Recent studies have founded the skeletal muscle works as an organ with immune regulatory properties by generating myokines which have anti-inflammatory and immunoprotective effects.^{41,44} However, the direct causation between BMI and mortality is unknown and the cause of death in these patients needs to be analyzed in the future.

The cornerstones of cardiorenal protection for patients with DM and ASCVD are blockade of the RAAS and control of hyperglycemia, hypertension, and atherogenic dyslipidemia.¹⁵ The most common cause of mortality in patients with CKD and ASCVD is sudden cardiac death that can primarily be attributed to ventricular arrhythmia.¹⁴ Measures to prevent rapid volume changes and address electrolyte imbalances may prove beneficial for these patients.¹⁴ Prolonged diuretic use has been reported to be associated with activation of the RAAS/sympathetic system, hypotension, insufficient plasma volume, and increased blood viscosity and is potentially harmful for patients with DM, ASCVD and CKD.^{45,46} This finding highlights the importance of individualized fluid management strategies, with careful monitoring of kidney function and electrolyte levels in this high-risk population. Few studies have directly analyzed this patient group, and those investigating RAAS inhibitors in patients with DM, CKD and ASCVD have reported conflicting results.^{47–50} Although research has reported exposure to RAAS inhibitors after AKI to be associated with reduced risks of mortality and progression to incident CKD,⁵¹ further investigations are required to expand the academic understanding in this area. Sodium-glucose transport protein 2 inhibitors (SGLT-2is) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are approved antidiabetic medications with documented beneficial effects in reducing cardiorenal risk.^{49,52,53} Nevertheless, evidence supporting the positive effects of GLP-1 RAs on advanced CKD outcomes is limited.^{49,54} The American Diabetes Association recommends the use of SGLT-2is or GLP-1 RAs for patients with DM who also have ASCVD, CKD, or CHF.^{49,55} The CKD clinical guideline also recommend SGLT-2is for patients with DM, CKD, and eGFR ≥ 20 mL/min/1.73 m² with or without uACR ≥ 200 mg/g or CHF.⁵⁵ The same guidelines recommend the use of GLP-1 RAs in diabetic patients with CKD who have not achieved glycemic targets despite the use of metformin and SGLT-2 is or who are unable to use those medications.⁵⁵ Recent outcome trials have demonstrated significant reductions in cardiorenal risk and prevention of AKI-induced CKD resulting from administration of nonsteroidal mineralocorticoid receptor antagonists (MRAs) such as finerenone.^{49,55} In the standpoint of AoCKD mechanistic insights, the role of SGLT-2is, GLP-1 RAs and nonsteroidal MRAs are beneficial to cardiorenal protection.^{56–58} Furthermore, current treatment options offer only modest benefits, and clinicians are not consistently able to rigorously monitor and control risk factors in patients with DM, ASCVD and renal dysfunction, resulting in a substantial residual cardio-kidney-metabolic risk. These findings reinforce the importance of optimizing pharmacologic therapy in diabetic patients with renal dysfunction to improve long-term clinical outcomes. Interestingly, in the AoCKD cohort, LVEF was not associated with any adverse outcomes in comparison with NKD cohort (Table 6). Besides, the mean LVEF in AoCKD cohort was 64.30 ± 12.31 (>40%) (Table 3). The potential usefulness of speckle tracking echocardiography (STE) for early detecting subclinical myocardial dysfunction and providing prognostic information, defined as the impairment of left ventricular (LV) global longitudinal strain (GLS) in the presence of LVEF >40% in the ASCVD settings.⁵⁹ Prospective studies incorporating LV-GLS assessment by STE methodology could provide valuable insights into its utility for early detection and risk stratification, potentially leading to improved clinical outcomes. In summary, we have incorporated our analyzed data to expand on prior findings and summarize potential clinical suggestions (Table 7).

The strengths of this study include its large sample obtained from the TMUCRD and its use of longitudinal models. Additionally, this study investigated evidence regarding the impact of AKI on the post-ASCVD recurrent cardiovascular events in patients with DM. Despite the strengths and the novelty, certain limitations should be acknowledged. First, data

Table 7 Summary of Clinical Recommendations for DM Patients With Renal Dysfunction Following ASCVD Events

| DM Patients with Kidney Dysfunction | Recommendation Grade of Nephrologist Consultation | Potential Associated Indicator of Prognosis | Echocardiography (LVEF, LV-GLS Assessment) | Medications: Recommendation (Statin, Metformin, SGLT-2is, GLP-1 RAs, Nonsteroidal MRAs) or Cautious Use (Diuretics) |
|-------------------------------------|---|---|--|---|
| AoCKD | Very strong | Age, BMI, uACR | LVEF, LV-GLS | Metformin, diuretics, SGLT-2is, GLP-1 RAs, nonsteroidal MRAs |
| CKD | Strong | Age, BMI, uACR | LVEF, LV-GLS | Statin, metformin, diuretics, SGLT-2is, GLP-1 RAs, nonsteroidal MRAs |
| AKI | Weak | LVEF, uACR | LVEF | Diuretics, SGLT-2is |

Abbreviations: DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; AoCKD, acute-on-CKD; BMI, body mass index; uACR, urine albumin-to-creatinine ratio; LV-GLS, left ventricular global longitudinal strain; SGLT-2is, sodium-glucose transport protein 2 inhibitors; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; MRAs, mineralocorticoid receptor antagonists; CKD, chronic kidney disease; AKI, acute kidney injury; LVEF, left ventricular ejection fraction.

regarding lifestyle and personal habits (such as current smoker, functional status) were unavailable in TMUCRD. Second, this was an observational real-world study, and therefore, it may be subject to bias due to unmeasured confounders. Some confounding factor such as variations in prescription drug preferences and limitations; genetic disposition toward AKI, CKD, or ASCVD; and possible fluctuations between different stages of CKD over time may exist. However, the study design is appropriate for situations in which a randomized controlled trial is impractical. Furthermore, our data should be interpreted cautiously considering the retrospective design. The primary goal of this study was to establish the association between renal dysfunction and subsequent cardiovascular events. Finally, the generalizability of our results may be limited to Taiwan and other Asian countries.

Conclusions

The study demonstrates that in patients with DM, the occurrence of AKI (superimposed on CKD) during their ASCVD event was associated with significantly higher short-term mortality and adverse cardiovascular outcomes. The overlap between AKI and CKD is often unrecognized, with its clinical significance underestimated in primary care settings. However, our findings underscore its importance and highlight the need for a longitudinal follow-up and proactive management in diabetic patients with ASCVD events and coexisting renal dysfunction. These findings highlight the need for dedicated case-managed, personalized and multidisciplinary interventions for cardiorenal health. The early nephrologist consultation, routine renal and cardiovascular monitoring, echocardiography with speckle-tracking strain, urine albumin-to-creatinine ratio, pharmacologic strategies, such as cautious use of diuretics, use of sodium-glucose transport protein 2 inhibitors, statin or metformin are recommended to improve outcomes in this high-risk group. Further prospective studies are warranted to confirm the effectiveness of comprehensive management in this group of patients.

Abbreviations

ASCVD, Atherosclerotic cardiovascular disease; AMI, acute myocardial infarction; AKI, acute kidney injury; AoCKD, acute-on-CKD; aHRs, adjusted HRs; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; CIs, confidence intervals; DM, diabetes mellitus; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HRs, hazard ratios; NKD, no known kidney disease; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; MRAs, mineralocorticoid receptor antagonists; PAOD, peripheral artery occlusive disease; PS, propensity score; SGLT-2is, sodium-glucose transport protein 2 inhibitors; TMUCRD, Taipei Medical University Clinical Research Database; uACR, urine albumin-to-creatinine ratio.

Data Sharing Statement

All relevant data supporting the conclusions of this article are included within the manuscript.

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Disclosure

The authors declare that they have no conflicts of interest to disclose in this work.

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